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(54) Title: THERAPEUTIC DELIVERY OF CARBON MONOXIDE

(57) Abstract: Compounds, pharmaceutical compositions and methods for the therapeutic delivery of carbon monoxide to humans and other mammals that employ transition metal complexes having at least a substituted cyclopentadienyl, indenyl or fluorenyl ligand and two or more carbonyl ligands.

WO 2007/085806 A2

Therapeutic delivery of carbon monoxide

FIELD OF THE INVENTION

5           The present invention relates to compounds,  
pharmaceutical compositions and methods for the therapeutic  
delivery of carbon monoxide to humans and other mammals.  
Another use of the compositions and compounds is for organ  
perfusion. In particular, the invention also relates to  
10       methods, compounds and pharmaceutical compositions for carbon  
monoxide delivery to extracorporeal and isolated organs of  
humans and other mammals.

BACKGROUND OF THE INVENTION

15           Carbon monoxide (CO) is, by common definition, a  
colourless, odourless, tasteless, non-corrosive gas of about  
the same density as that of air and is the most commonly  
encountered and pervasive poison in our environment. Depending  
on the extent and time of exposure, CO is capable of producing  
20       a myriad of debilitating and harmful residual effects to the  
organism (1). The most immediate of these effects, and perhaps  
the most notorious one, is binding to hemoglobin in the blood  
stream, which rapidly decreases the oxygen transport  
capability of the cardiovascular system.

25           Paradoxically, more than half a century ago it was found  
that CO is constantly formed in humans in small quantities  
(2), and that under certain pathophysiological conditions this  
endogenous production of CO may be considerably increased (3-  
5). The discovery that hemoglobin, a heme-dependent protein,  
30       is required as substrate for the production of CO in vivo  
(6,7) and the identification of the enzyme heme oxygenase as  
the crucial pathway for the generation of this gaseous  
molecule in mammals (8) set the basis for the early  
investigation of an unexpected and still unrecognized role of  
35       CO in the vasculature (9).

A discussion of the background studies carried out in

this area are reported in the publication WO 02/092075, which originates from the work of some of the present inventors. The beneficial physiological effects of carbon monoxide (CO) has also been recognized and reported in a number of other publications. As a consequence of these beneficial physiological effects, the literature contains many proposals and studies for providing methods or compounds that have use in delivering therapeutic quantities of carbon monoxide at an appropriate rate to a desired physiological site.

WO 2003/000114 (Beth Israel Deaconess Medical Center) describes a method involving the administration of a carbon monoxide-oxygen (O<sub>2</sub>) gaseous mixture to an organ, which helps to prevent organ damage for transplant procedures.

Similarly, WO 03/094932 (Yale University) discloses several methods for the generation of carbon monoxide gas and the subsequent administration of the gas to a patient for the treatment of various disorders.

WO 02/078684 (Sangstat Medical Corporation) discloses methods and pharmaceutical compositions for the treatment of vascular disease and for modulating inflammatory and immune processes by using methylene chloride as a carbon monoxide generating compound.

WO 02/092075 and WO 2004/045598, which originate from some of the present inventors, disclose metal carbonyls that are carbon monoxide releasing compounds (CORMs) for the therapeutic delivery of CO to an *in vivo* or an *ex vivo* physiological target site. Some of the transition metal carbonyl compounds disclosed in these publications are soluble in water, which is desirable for formulating a pharmaceutical composition. Not all of the compounds disclosed in these publications, such as the cyclopentadienyl iron-carbonyl compound [CpFe(CO)<sub>3</sub>]PF<sub>6</sub>, were found to be soluble in water. This particular compound was soluble in dimethylsulphoxide (DMSO) and produced a precipitate during release of CO.

Formation of a precipitate in biological system, whether before or after CO delivery to a physiological target, is

undesirable and may be toxic to the organism or result in harmful physiological side effects.

WO 98/029115 (University of British Columbia) discloses transition metal nitrosyl complexes for treating hypertension, angina pectoris and congestive heart disease. The compounds disclosed in this publication require the presence of at least one nitrosyl ligand coordinated to the metal.

Cyclopentadienyl metal carbonyl compounds of the form  $\text{CpM}(\text{CO})_2\text{NO}$  and  $\text{Cp}^*\text{M}(\text{CO})_2\text{NO}$ , where  $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ;  $\text{Cp}$  is a cyclopentadienyl ligand and  $\text{Cp}^*$  is a pentamethyl cyclopentadienyl ligand, are exemplified in this document.

US 2004/0116448 (Schmalz, H.-G. *et al*) discloses the use of iron carbonyl complexes for the treatment of diseases caused by highly proliferating cells, such as tumour cells. The active compounds contain a butadiene moiety, which is bound to an iron tricarbonyl unit in an  $\eta^4$  manner. The butadiene moiety may form part of a five membered cyclic ring. Generation of a cyclopentadienyl group and its subsequent coordination to the transition metal in an  $\eta^5$  manner is not disclosed.

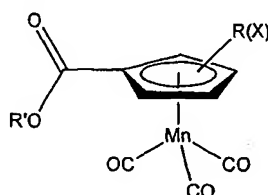
WO 03/066067 (Haas, W. *et al*) proposes as a class of compounds "CO containing organometallic complexes" for use in the treatment and/or prevention of diseases. Generic examples of organometallic transition metal-carbonyl compounds that fall within this class are described. Amongst these examples, the generic formulae for the following organometallic compounds are given:

- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_3]$  for  $\text{M} = \text{Mn}, \text{Re}$ ;
- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_2]$  for  $\text{M} = \text{Co}, \text{Rh}$ ;
- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_2\text{X}]$  for  $\text{M} = \text{Fe}, \text{Ru}$ ;
- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_3\text{X}]$  for  $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ;
- $[\eta^5\text{-IndM}(\text{CO})_2\text{X}]$  for  $\text{M} = \text{Fe}, \text{Ru}$ ;
- $[\eta^5\text{-IndM}(\text{CO})_3\text{X}]$  for  $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ;
- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_2\text{L}]^+\text{Y}^-$  for  $\text{M} = \text{Fe}, \text{Ru}$ ; and
- $[(\eta^5\text{-CpR})\text{M}(\text{CO})_3\text{L}]^+\text{Y}^-$  for  $\text{Cr}, \text{Mo}, \text{W}$ ;

where  $\text{Cp}$  is a cyclopentadienyl ligand,  $\text{Ind}$  is an indenyl

ligand, R is H, alkyl, acyl, formyl, carboxylate, sugar,  
 peptide or halide, X is alkyl, aryl, halide, OR', SR', O<sub>2</sub>CR',  
 S<sub>2</sub>CNR'<sub>2</sub>, S<sub>2</sub>P(OR')<sub>2</sub>, L is CO, olefin, alkyne, or a monodentate 2  
 5 electron donor of O, S, N or P, and Y is a halide or a weakly  
 coordinating anion.

Attaching a carboxylic derivative to the cyclopentadienyl  
 ring is also proposed in order to modify biological  
 compatibility and solubility. The following Mn complex is  
 given as an example of a possible modified compound:



10

where R(X) is H, alkyl, aryl, formyl, acyl, carboxylate or  
 fused C6 aromatic ring (indenyl ligand), and R' is H, alkyl,  
 peptide or sugar.

15

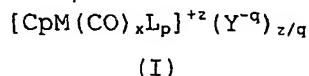
WO 03/066067 (Haas, W. et al) does not describe the  
 synthesis of any of the above compounds and does not contain  
 any literature reference to a procedure for their preparation.  
 It is further noted that there is no evidence in this  
 document, such as biological test data, in support of the use  
 of these compounds for the delivery of CO *in vivo* or *ex vivo*.

20

#### Statement of the invention

As exemplified by the data presented below, the present  
 inventors have found that pharmaceutical compositions and  
 compounds according to the invention can be used to deliver CO  
 25 to a physiological target and result in the formation of a by-  
 product or products that are soluble in an aqueous  
 physiological fluid after CO release.

Accordingly, a first aspect of the present invention  
 provides a pharmaceutical composition for delivery of CO,  
 30 comprising as an active ingredient a compound represented by  
 formula (I) or formula (II) below:



wherein:-

M is a transition metal selected from group 6, 7, 8 or 9 of the periodic table;

Y is a counteranion;

5 q is the charge of Y and is selected from 1, 2 or 3;

x is 2, 3 or 4;

z is 0 or 1, and x, z and p satisfy the equation

$$13 - g = 2x - z + p$$

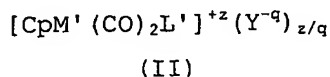
where g is the group number of M in the periodic table, and

10 where

p is 0 or 1 when g is 6; or

p is 0 when g is 7, 8 or 9;

L is a ligand selected from H, halide, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>6-14</sub> aryloxy, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, acyloxy  
 15 (-OC(=O)R<sup>5</sup>), amido (-C(=O)NR<sup>5</sup>R<sup>6</sup>), acylamido (-NR<sup>5</sup>C(=O)R<sup>6</sup>), aminocarbonyloxy (-OC(=O)NR<sup>5</sup>R<sup>6</sup>) and aminothiocabonylthiol (-SC(=S)NR<sup>5</sup>R<sup>6</sup>);



20 wherein

M' is Fe or Ru;

Y is a counteranion;

q is the charge of Y and is selected from 1, 2 or 3;

L' is a ligand selected from either

25 a first group consisting of H, halide, -NO<sub>2</sub>, -ONO, -ONO<sub>2</sub>, -OH, -SCN, -NCS, -OCN, -NCO, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>6-14</sub> aryloxy, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, acyloxy (-OC(=O)R<sup>7</sup>), amido (-C(=O)NR<sup>7</sup>R<sup>8</sup>), acylamido (-NR<sup>7</sup>C(=O)R<sup>8</sup>), aminocarbonyloxy (-OC(=O)NR<sup>7</sup>R<sup>8</sup>), (SC(=O)R<sup>7</sup>), -SC(S)R<sup>7</sup>, -SC(S)OR<sup>7</sup>, -SC(O)NR<sup>7</sup>R<sup>8</sup>,  
 30 -SC(O)OR<sup>7</sup>, aminothiocabonylthiol (-SC(=S)NR<sup>7</sup>R<sup>8</sup>), -OC(=S)R<sup>7</sup>, -N(C(=O)R<sup>7</sup>)<sub>2</sub>, and -C(O)(OR<sup>7</sup>); -O-PR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>, -O-PR<sup>7</sup><sub>3-n</sub>(OR<sup>8</sup>)<sub>n</sub> where n=1, 2 or 3, -O-PR<sup>7</sup><sub>(3-n)</sub>(NR<sup>8</sup>R<sup>9</sup>)<sub>n</sub> where n=1, 2 or 3; or

a second group consisting of OR<sup>7</sup>R<sup>8</sup>, O=CR<sup>7</sup>R<sup>8</sup>, O=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>, O=C(OR<sup>7</sup>)R<sup>8</sup>, O=SR<sup>7</sup>R<sup>8</sup>, O=S(O)R<sup>7</sup>R<sup>8</sup>, SR<sup>7</sup>R<sup>8</sup>, S(O)R<sup>7</sup>R<sup>8</sup>, S=CR<sup>7</sup>R<sup>8</sup>,  
 35 S=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>, S=C(OR<sup>7</sup>)R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>, NCR<sup>7</sup>, N\* where N is an aromatic nitrogen atom in an aromatic ring represented by N\*, PR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>,

$\text{PR}^7_{(3-n)}(\text{OR}^8)_n$  where  $n=1, 2$  or  $3$ ,  $\text{PR}^7_{(3-n)}(\text{NR}^8\text{R}^9)_n$  where  $n=1, 2$  or  $3$ ,  
 $\text{O}=\text{PR}^7\text{R}^8\text{R}^9$ ,

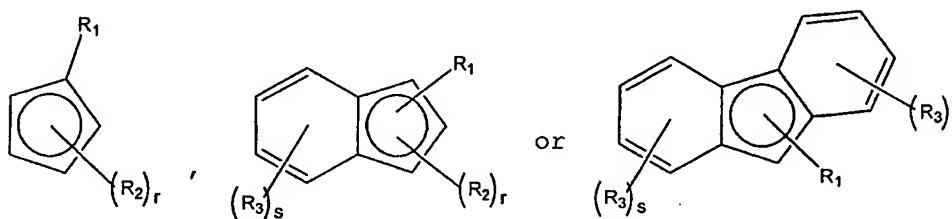
$\text{O}=\text{PR}^7_{(3-n)}(\text{OR}^8)_n$  where  $n=1, 2$  or  $3$ ,  $\text{O}=\text{PR}^7_{(3-n)}(\text{NR}^8\text{R}^9)_n$  where  $n=1, 2$   
 or  $3$ ;

- 5  $\text{R}^7$ ,  $\text{R}^8$  and  $\text{R}^9$  are independently selected from H, optionally substituted  $\text{C}_{1-7}$  alkyl and optionally substituted  $\text{C}_{6-20}$  aryl, with the proviso that any two of  $\text{R}^7$ ,  $\text{R}^8$  and  $\text{R}^9$  which are both attached to the same O, N or S atom may, taken together with that atom, form an optionally substituted heterocyclic ring  
 10 having 5, 6 or 7 ring atoms;

$z=0$  when  $\text{L}'$  is from said first group and  $z=1$  when  $\text{L}'$  is from said second group;

and wherein in formula (I) and formula (II):-

Cp is selected from:



- 15 where  $r$ ,  $s$  and  $t$  are each independently selected from 1, 2, 3 or 4; and

$\text{R}_1$  is either:

$-\text{[Alk]}_n-\text{O}-\text{C}(\text{O})-\text{Q}_1$ ,  $-\text{[Alk]}_n-\text{C}(\text{O})-\text{O}-\text{Q}_1$ ,  $-\text{[Alk]}_n-\text{NR}_4-\text{C}(\text{O})-\text{Q}_1$  or  
 $-\text{[Alk]}_n-\text{C}(\text{O})-\text{NQ}_1\text{Q}_2$ ,

- 20  $n$  is 0 or 1;

Alk is a  $\text{C}_{1-28}$  alkylene group;

$\text{Q}_1$  and  $\text{Q}_2$  are each independently selected from H, optionally substituted  $\text{C}_{1-22}$  alkyl and an optionally substituted  $\text{C}_{6-25}$  aryl group;

- 25 each  $\text{R}_2$  is independently selected from  $\text{R}_1$ , H,  $\text{C}_{1-22}$  alkyl,  $\text{C}_{6-25}$  aryl,  $\text{C}_{1-7}$  alkoxy,  $\text{C}_{5-10}$  aryloxy, halide, formyl,  $\text{C}_{1-7}$  alkylacyl and  $\text{C}_{6-20}$  arylacyl;

$\text{R}_4$  is selected from H,  $\text{C}_{1-22}$  alkyl and  $\text{C}_{6-25}$  aryl;

- each  $\text{R}_3$  is independently selected from H, hydroxy, nitro,  
 30 cyano, halide, sulfhydryl,  $\text{C}_{1-22}$  alkyl,  $\text{C}_{6-25}$  aryl,  $\text{C}_{1-7}$  alkoxy,

C<sub>5-10</sub> aryloxy, formyl, C<sub>1-7</sub> alkylacyl, C<sub>6-20</sub> arylacyl, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, carboxylic acid (-C(=O)OH), ester (-C(=O)OR<sup>5</sup>), acyloxy (-OC(=O)R<sup>5</sup>), amido (-C(=O)NR<sup>5</sup>R<sup>6</sup>), acylamido (-NR<sup>5</sup>C(=O)R<sup>6</sup>) and amino (-NR<sup>5</sup>R<sup>6</sup>); and  
5 R<sup>5</sup> and R<sup>6</sup> are independently selected from H, C<sub>1-7</sub> alkyl and C<sub>6-20</sub> aryl.

The transition metal carbonyl compounds in pharmaceutical compositions according to the first aspect of the invention comprise carbonyl ligands and a cyclopentadienyl, indenyl or  
10 fluorenyl ligand covalently bonded to the transition metal centre in an  $\eta^5$  manner. These organometallic compounds satisfy what is commonly known in the art as the 18 electron rule.

Before taking into account any electron contribution from the coordination of a ligand, the transition metal in  
15 pharmaceutical compositions or compounds of the present invention already has some electrons in its valence shell. The number of electrons already present is given by the group number of the transition metal in the periodic table. In this specification the groups of the periodic table are numbered  
20 according to the IUPAC system from 1 to 18. The cyclopentadienyl, indenyl or fluorenyl ligand bonds to the transition metal by its  $\pi$  orbitals in an  $\eta^5$  manner, such that it contributes five electrons to the valence shell of the metal. Each carbonyl ligand formally donates two electrons to  
25 the valence shell of the transition metal. A ligand L, as written in formula (I) above, may also be coordinated to the metal. L represents an anionic ligand, such as I<sup>-</sup>, and formally contributes one electron to the valence shell of the metal. The total number of carbonyl ligands and L ligands  
30 that coordinate to the metal is determined by the 18 electron rule.

If the transition metal is selected from a group in the periodic table such that it has an even number of electrons i.e.  $g = 6$  or  $8$ , and there are no L ligands (one electron  
35 anionic ligands) coordinated to the metal, then to satisfy the 18 electron rule the organometallic complex will have a formal



charge of +1 because it must lose an electron. Alternatively, when g is 6, one of the carbonyl ligands (a two electron donor) may be replaced with an L ligand (a one electron donor). In such compounds the organometallic complex is not charged.

The oxidation state of the transition metal in compounds of the present invention from group 6 or 8 of the periodic table is +2. Whereas, the oxidation state of the transition metal from group 7 or 9 of the periodic table in compounds according to the present invention is +1.

The same principles apply for the compounds of formula (II). The oxidation state of Fe or Ru is +2.

Attaching substituents to the cyclopentadienyl, indenyl or fluorenyl ring of a transition metal complex may subtly alter the electronic properties of the molecule. Thus the inclusion of particular types of substituent may allow modulation of the rate of CO release to a physiological target from the carbon monoxide releasing molecule (CORM). The chemical nature of the substituent may additionally increase the solubility of the CORM in aqueous physiological fluid.

WO 03/066067 (Haas, W. et al) suggests that several classes of organometallic compound may be used as CORMs. However, WO 03/066067 does not contain an enabling disclosure for many of these classes of organometallic compound. Furthermore, this document provides no data in support of these molecules as being CORMs, but rather speculates, what would have been known to the skilled worker in the art, that these classes of compounds are potential CORM candidates. The present inventors have found that under the conditions of the tests that they employed, several classes of organometallic compounds that are proposed for use as CORMs in WO 03/066067 do not actually release CO to a physiological target.

The present inventors surprisingly found that compounds according to the present invention do not precipitate in an aqueous physiological fluid after release of CO. It is believed that the presence of the substituent ( $R_1$ ) on the

cyclopentadienyl ring increases the solubility and/or stabilises the resulting CORM by-product thereby preventing decomposition to an insoluble species. Formation of an insoluble by-product or products within a biological system may cause undesirable physiological effects.

If the transition metal is selected from group 6 or 8 of the periodic table, then in order to satisfy the 18 electron rule, the organometallic compound according to the present invention has a transition metal in the +2 oxidation state. When  $p = 0$ , such that no L ligands are present, the compound will be charged i.e.  $z = 1$  in formula (I) above. The resulting ionic compound will consist of an organometallic cation, and a counter anion represented by Y in formula (I) above.

It is predicted that the CORM by-products of compounds of formula (I) having a transition metal in the +2 oxidation state (i.e.  $g = 6$  or  $8$ ) and compounds of formula (II) will have greater solubility in an aqueous physiological fluid than the CORM by-products of compounds with a metal in the +1 oxidation state. Preferably, the oxidation state of the transition metal is +2. In particular, solubility in an aqueous physiological fluid is likely to be greater for compounds where the transition metal is in the +2 oxidation state and has a formal charge of +1 ( $z = 1$ ).

If the organometallic complex has a formal charge, then it will be associated with a counteranion. The counteranion, represented in formula (I) and (II) above by Y, may have a negative charge greater than or equal to 1, as represented by "q". According to the present invention, the charge of the organometallic cation cannot exceed +1 (unless for example a ligand or constituent contains a quaternary nitrogen). If the charge of counteranion exceeds -1, then to balance the charge of the overall compound, there must be more than one organometallic cation. For example, if the counteranion is sulphate ( $\text{SO}_4^{2-}$ ) and the cation is  $[\text{CpFe}(\text{CO})_3]^{+1}$ , then the formula of the compound may be written as  $[\text{CpFe}(\text{CO})_3]_2(\text{SO}_4)$  and

is represented in formula (I) above in terms of a single organometallic cation as  $[\text{CpFe}(\text{CO})_3](\text{SO}_4)_{1/2}$ .

It is preferred that the counteranion is selected from a halide (e.g.  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$  or  $\text{I}^-$ ); sulphonate (e.g.  $\text{TsO}^-$ ,  $\text{MsO}^-$ ,  $\text{TfO}^-$ ,  $\text{BsO}^-$ ); borate (e.g.  $\text{BF}_4^-$ ,  $\text{BPh}_4^-$ ); hexafluorophosphate ( $\text{PF}_6^-$ ); a perhalate (e.g.  $\text{ClO}_4^-$ ); sulphate ( $\text{SO}_4^{2-}$ ); phosphate ( $\text{PO}_4^{3-}$ ); a carboxylate anion of an organic acid, such as the anions of the acids 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedithiolic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric; or of an amino acid, such as glycinate etc., or any other pharmaceutically acceptable anion known to those skilled in the art, such as those described in S Berge et al, Journal of Pharmaceutical Science (1977), 66 (1) 1-19; P Gould, International Journal of Pharmaceutics (1986), 33, 201-217. Most preferred are counteranions that are carboxylate anions of organic carboxylic acids or amino acids.

When the transition metal is from group 6, the metal may be coordinated to four carbonyl ligands so that the resulting organometallic compound is cationic having a charge of +1. Alternatively, the group 6 transition metal may be neutral if it is coordinated to three carbonyl groups and an anionic ligand represented by L. If the transition metal is from group 6, then it is preferred that p is 1 and x is 3 so that the transition metal is coordinated to an L ligand. L is selected from H, halide,  $\text{C}_{1-7}$  alkyl,  $\text{C}_{6-14}$  aryl,  $\text{C}_{1-7}$  alkoxy,  $\text{C}_{6-14}$  aryloxy,  $\text{C}_{1-7}$  alkylthio,  $\text{C}_{5-10}$  arylthio, acyloxy ( $-\text{OC}(=\text{O})\text{R}^5$ ), amido ( $-\text{C}(=\text{O})\text{NR}^5\text{R}^6$ ), acylamido ( $-\text{NR}^5\text{C}(=\text{O})\text{R}^6$ ), aminocarbonyloxy ( $-\text{OC}(=\text{O})\text{NR}^5\text{R}^6$ ) and aminothiocabonylthiol ( $-\text{SC}(=\text{S})\text{NR}^5\text{R}^6$ ). In particular, L is selected from H, halide,  $\text{C}_{1-7}$  alkyl,  $\text{C}_{6-14}$  aryl,

C<sub>1-7</sub> alkoxy and C<sub>6-14</sub> aryloxy. More preferably, L is H, halide, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl. Most preferred is when L is Cl, Br or I.

Some of the transition metals in groups 6 to 9 may cause or be associated with undesirable physiological side effects.

5 Preferably, the transition metal M is selected from Fe, Ru, Mn and Mo. Most preferred are compounds where M is one of Fe and Mo. Fe is particularly preferred.

In the compound of formula (II), M' is preferably Fe. The L' is selected from the first group of anionic (one  
10 electron donor) ligands or from the second group of neutral (two electron donor) ligands.

Among the ligands of the first group, preferred are H, halide, -NO<sub>2</sub>, -ONO-, -ONO<sub>2</sub>, -OH, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>1-7</sub> alkoxy and C<sub>6-14</sub> aryloxy. More preferably L' of the first group  
15 is halide, -NO<sub>2</sub>, -ONO, -ONO<sub>2</sub>, -OH, C<sub>1-7</sub> alkyl or C<sub>6-14</sub> aryl. Most preferred are Cl, Br, I and -ONO<sub>2</sub>.

The ligands of the second group coordinate through O, S, N or P. In each item of the list of ligands of the second group, the coordinating atom is placed first. Particular  
20 examples of the ligands of the second group are

OH<sub>2</sub> (water)

OHR<sup>7</sup>, e.g. C<sub>2</sub>H<sub>5</sub>OH

OR<sup>7</sup>R<sup>8</sup>, e.g. tetrahydrofuran

O=CR<sup>7</sup>R<sup>8</sup>, e.g. (CH<sub>3</sub>)<sub>2</sub>CO

25 O=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>, e.g. CH<sub>3</sub>CON(CH<sub>3</sub>)<sub>2</sub>

O=C(OR<sup>7</sup>)R<sup>8</sup>, e.g. CH<sub>3</sub>COOCH<sub>3</sub>

O=SR<sup>7</sup>R<sup>8</sup>, e.g. DMSO

O=S(O)R<sup>7</sup>R<sup>8</sup>, e.g. (CH<sub>3</sub>)<sub>2</sub>SO<sub>2</sub>

SH<sub>2</sub>

30 HSR<sup>7</sup>

SR<sup>7</sup>R<sup>8</sup>.

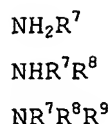
S(o)R<sup>7</sup>R<sup>8</sup>, e.g. DMSO coordinating through S

S=CR<sup>7</sup>R<sup>8</sup>, e.g. (CH<sub>3</sub>)<sub>2</sub>CS

S=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>, e.g. CH<sub>3</sub>C(S)N(CH<sub>3</sub>)<sub>2</sub>

35 S=C(OR<sup>7</sup>)R<sup>8</sup>, e.g. CH<sub>3</sub>C(S)OCH<sub>3</sub>

NH<sub>3</sub>



a ligand of the type N\* coordinating through an sp<sup>2</sup>N  
 5 in an aromatic ring, e.g. pyridine, histidine or adamine.

In pharmaceutical compositions according to the present invention, the compounds represented by formula (I) or formula (II) contain an ester or amide group in the substituent R<sup>1</sup> which is attached to the cyclopentadienyl, indenyl or  
 10 fluorenyl ring. It is shown herein that the selected compounds release CO to a biological system and that the starting compound is soluble in an aqueous physiological fluid. The inventors have surprisingly found that coupling the cyclopentadienyl, indenyl or fluorenyl ring to an ester or  
 15 amide group confers additional solubility and/or stability to the by-product or by-products formed after CO release.

The R<sup>1</sup> substituent attached to the Cp group comprises an ester group, represented by -[Alk]<sub>n</sub>-O-C(O)-Q<sub>1</sub> or -[Alk]<sub>n</sub>-C(O)-O-Q<sub>1</sub>, or an amide group, as represented by -[Alk]<sub>n</sub>-NR<sub>4</sub>-C(O)-Q<sub>1</sub> or  
 20 -[Alk]<sub>n</sub>-C(O)-NQ<sub>1</sub>Q<sub>2</sub>. It is preferred that R<sup>1</sup> is an ester group -[Alk]<sub>n</sub>-O-C(O)-Q<sub>1</sub> or -[Alk]<sub>n</sub>-C(O)-O-Q<sub>1</sub>.

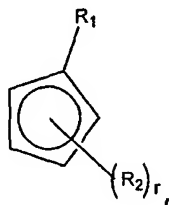
In an embodiment of the present aspect of the invention, R<sup>1</sup> is a -[Alk]<sub>n</sub>-O-C(O)-Q<sub>1</sub> unit, where the ester unit is attached by its "alkoxy" oxygen atom to the Cp group either directly or  
 25 by an alkylene spacer unit, which is represented by "Alk". In this embodiment, it is preferred for an alkylene spacer unit to be present i.e. n = 1. It is believed that solubility of the by-product or products formed after CO release are more soluble and/or stable when the ester group is attached by its  
 30 oxygen to an alkylene spacer and then to the Cp group. Furthermore, compounds having an ester group attached to the Cp ring by an alkylene spacer group are synthetically more accessible.

In this particular embodiment, the alkylene spacer unit  
 35 "Alk" is a C<sub>1-28</sub> alkylene group. It is preferred that "Alk" is a linear or branched saturated C<sub>1-10</sub> alkylene group, which

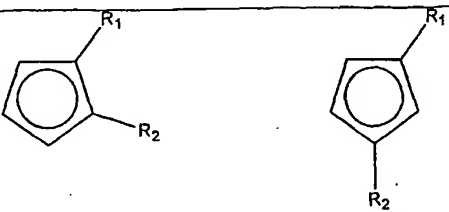
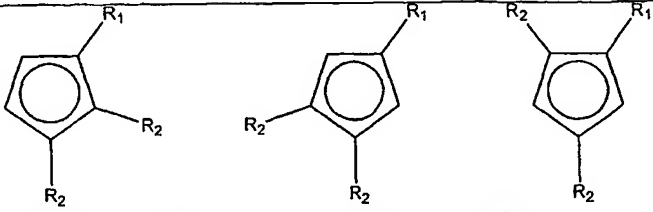
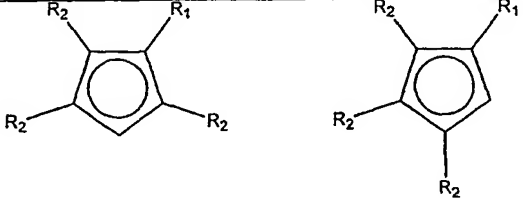
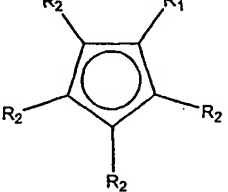
excludes the subclasses alkenylene, alkynylene and cycloalkylene. In particular, it is preferable that "Alk" is an unbranched or linear saturated C<sub>1-6</sub> alkylene group. More preferably, "Alk" is an unbranched and unsubstituted C<sub>2-5</sub> alkylene group.

In an alternative embodiment, R<sup>1</sup> is -[Alk]<sub>n</sub>-C(O)-O-Q<sub>1</sub>, where the ester group is attached by an optional alkylene spacer unit by its carbonyl carbon atom to the Cp group. When the ester group is attached to the Cp group in this manner, the optional alkylene spacer has less of an effect on the solubility of the by-product or products from the CORM. However, it is believed that in this and the previous embodiment, the length of the alkylene spacer may have a modulating effect in the CO releasing properties of the CORM molecule and has a stabilising effect on the CORM by-product or products. When n is 1, "Alk" is preferably linear or branched saturated C<sub>1-10</sub> alkylene group, which excludes the subclasses alkenylene, alkynylene and cycloalkylene. It is further preferred that "Alk" is a linear or unbranched saturated C<sub>1-6</sub> alkylene group or more preferably a C<sub>1-5</sub> alkylene group. Most preferred is when "Alk" is a linear saturated C<sub>1-4</sub> alkylene group.

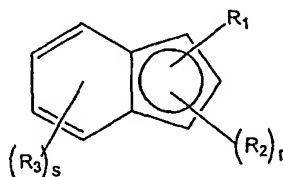
When Cp represents the ligand



the number of R<sub>2</sub> substituents is given by r and can be 1, 2, 3 or 4. When r is 1, 2 or 3 there are several possible stereoisomers where the position of the R<sub>2</sub> substituent(s) varies relative to the position of R<sub>1</sub>. The structural representation given above encompasses all of these possible stereoisomers, which are shown in the table below.

r	Stereoisomers	
1		
2		
3		
4		

Substituents, represented by  $R_3$ , may also be directly  
 5 attached to the aryl ring or rings of the indenyl or fluorenyl  
 ligand. For indenyl ligands, the label  $(R_3)_s$  in the structure  
 below, as used herein, includes indenyl ligands having one,  
 two, three or four  $R^3$  substituents attached to the phenyl or  
 aryl ring.

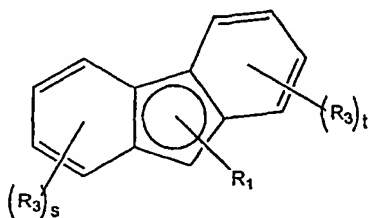


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The structural representation above encompasses all possible  
 isomers for each possible number of  $R_3$  aryl ring substituents.  
 For example, if there are two  $R_3$  substituents, then the

structural formula above includes the 4,5, 4,6, 4,7, 5,6, 5,7 and 6,7 isomers.

Similarly, the labels  $(R_3)_s$  and  $(R_3)_t$  each represent fluorenyl ligands having one, two, three or four  $R_3$  substituents attached to each of the respective aryl rings. The structural representation below also encompasses all possible  $R_3$  aryl ring substituent isomers, as described above for the indenyl ligand.



Each  $R_3$  aryl ring substituted may be independently selected from H, hydroxy, nitro, cyano, halide, sulfhydryl,  $C_{1-22}$  alkyl,  $C_{6-25}$  aryl,  $C_{1-7}$  alkoxy,  $C_{5-10}$  aryloxy, formyl,  $C_{1-7}$  alkylacyl,  $C_{6-20}$  arylacyl,  $C_{1-7}$  alkylthio,  $C_{5-10}$  arylthio, carboxylic acid ( $-C(=O)OH$ ), ester ( $-C(=O)OR^5$ ), acyloxy ( $-OC(=O)R^5$ ), amido ( $-C(=O)NR^5R^6$ ), acylamido ( $-NR^5C(=O)R^6$ ) and amino ( $-NR^5R^6$ ), where  $R^5$  and  $R^6$  are independently selected from H,  $C_{1-7}$  alkyl and  $C_{6-20}$  aryl. Preferably,  $R_3$  is selected from H, hydroxy, nitro, cyano, halide,  $C_{1-22}$  alkyl,  $C_{6-25}$  aryl,  $C_{1-7}$  alkoxy,  $C_{5-10}$  aryloxy and amino ( $-NR^5R^6$ ). More preferably,  $R_3$  is H, halide,  $C_{1-22}$  alkyl and  $C_{6-25}$  aryl. In particular,  $R_3$  is H, methyl, ethyl or phenyl. Most particularly,  $R_3$  is H.

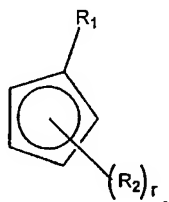
The number of  $R_3$  aryl ring substituents may vary, depending on the nature of the Cp group, from 1 to 8. It is preferred that there are one, two or three  $R_3$  aryl ring substituents. More preferred are indenyl or fluorenyl ligands where there are a total of one or two  $R_3$  aryl ring substituents.

When two or more substituents ( $R_1$ ,  $R_2$  or  $R_3$ ) are attached to the Cp group (the cyclopentadienyl, indenyl and fluorenyl ligand) of a transition metal carbonyl complex, the resulting organometallic carbonyl compound may have a chiral centre. Unless otherwise specified, a reference to a particular



compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g. asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

In another embodiment of the first aspect of the invention, it is preferred that Cp in the compound represented by formula (I) or formula (II) is

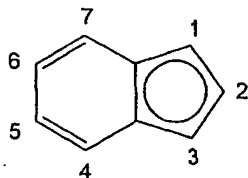


There have been many studies in the field of organometallic chemistry on the effect that substituents attached to the cyclopentadienyl ring have on the metal complex. As a result, the scientific literature in this field contains many synthetic methodologies for preparing substituted cyclopentadienyl rings. It is preferred that the cyclopentadienyl ring contains one or four  $R_2$  substituents i.e.  $r = 1$  or  $4$ . More preferably,  $r = 1$ . If the cyclopentadienyl ring contains a single  $R_2$  substituent when  $r = 1$ , then  $R_2$  will be in the 2- or 3- position relative to  $R_1$  on the cyclopentadienyl ring. Often cyclopentadienyl compounds having two substituents attached to the ring (i.e. 1, 2 or 1, 3 substituents) have to be separated by chromatography.

In yet another embodiment of the invention, it is preferred that the Cp ligand in formula (I) or formula (II) above is an indenyl ligand. The indenyl ligand contains a cyclopentadienyl ring fused at one side to a phenyl ring. The uncoordinated indenyl anion is a 10 electron aromatic system, compared to the 6 electron aromatic ring of the cyclopentadienide anion. This difference in the electronic properties of the indenyl ligand may subtly alter the electronic properties of the organometallic complex upon

coordination which, in turn, may effect the rate of CO release. In addition to this electronic effect, the additional arene ring may shield or provide a steric barrier. It is possible that this could increase the kinetic stability of CORMs containing an indenyl ligand. It is also well known in the art, that the bonding mode or hapticity of the indenyl ligands may change during a reaction, such as a ring slippage where the hapticity of the ligand can change from  $\eta^5$  to  $\eta^3$ . The change in bonding mode may aid the rate of reaction of the CORM in a physiological environment and thereby alter the rate of CO release.

In embodiments where the Cp group is an indenyl ligand, the  $R_1$  substituent is attached to the five-membered cyclopentadienyl-type ring of the indenyl ligand.  $R_1$  may be attached to the 1, 2 or 3 positions of the indenyl ligand, as indicated in the diagram.



The position of  $R_1$  on the indenyl ring may favour particular synthetic methods used for the preparation of the ligand. For example,  $R_1$  may be introduced into the 2-position of the indenyl ligand by using a starting material such as indanone. A maximum of two  $R_2$  substituents can be attached to the cyclopentadienyl moiety of the indenyl system. Preferably,  $r$  is 1.

In the embodiments where Cp is a cyclopentadienyl or an indenyl ligand, the five membered ring or cyclopentadienyl moiety may contain more than one substituent ( $R_1$  and  $R_2$ ). The second substituent may be incorporated onto the ligand to further aid the solubility of the CORM, the CORM by-product or may further assist in the modulation of the rate of CO release by the CORM compound.

The second substituent  $R_2$  may be independently selected from any of the groups for  $R_1$ . If  $R_2$  is selected from any of

the groups for  $R_1$ ,  $R_2$  is not limited so that it is identical to the group selected for  $R_1$ . However, it is preferable that if  $R_2$  is to be independently selected from a group for  $R_1$ , that  $R_2$  and  $R_1$  are identical. For example, when  $R_1$  is  $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{Me}$  then  $R_2$  is  $-\text{CH}_2-\text{O}-\text{C}(\text{O})-\text{Me}$ . If  $R_2$  is not selected from the groups defined for  $R_1$ , it is preferred that  $R_2$  is selected from H,  $\text{C}_{1-22}$  alkyl and  $\text{C}_{9-25}$  aryl. Most preferably  $R_2$  is H or methyl, more particularly H.

In addition to increasing the solubility, the inventors believe that the presence of the ester or amide group as a substituent on the Cp group may enhance or accelerate the rate of CO release in some physiological environments. Some of these environments enzymes, such as esterases, which are capable of hydrolysing the ester or amide group in compounds and pharmaceutical compositions of the present invention. Hydrolysis of the ester or amide group may result in the formation of a nucleophilic species, such as a carboxylate moiety, that is able to "attack" the metal centre and thereby trigger CO release from the CORM compound.

The inventors also believe that the length of the  $R_1$  Cp-substituent has a stabilising effect on the CORM by-product or products. The inventors propose that the carbonyl-oxygen atom of the ester or amide group may coordinate and thereby stabilise the transition metal centre after CO release. In principle, coordination may be to the metal centre of another, nearby molecule (intermolecular coordination) or to the metal of that same molecule (intramolecular coordination). In particular, when the ester or amide group is attached to the Cp unit by an alkylene spacer group, the carbonyl-oxygen atom may be able to "reach round" and coordinate to the metal in an intramolecular manner so that the overall ligand forms a chelate.

An alternative to the stabilising effect that may be provided by intramolecular coordination of the carbonyl oxygen atom, the  $Q_1$  and/or  $Q_2$  group that forms part of the  $R_1$  substituent may contain an atom or group that may coordinate

to the metal centre. This atom or group, may be a ligating atom or group and may preferentially coordinate to the metal instead of the carbonyl oxygen atom. Ligating atoms or groups are atoms or chemical functional groups that can coordinate as a ligand to a metal. Typically, the ligating atom or group has a lone pair of electrons or has a negative charge, which allows it to coordinate to the metal.

Preferential coordination of the ligating atom or group of  $Q_1$  and/or  $Q_2$  may occur when the overall length of  $R_1$  is too short for the carbonyl oxygen atom to reach the metal centre to coordinate in a intramolecular manner, or if the ligating part of the  $Q_1$  and/or  $Q_2$  group forms a stronger bond with the metal than the carbonyl oxygen atom.

In pharmaceutical compositions and compounds according to the present invention  $Q_1$  and  $Q_2$  are each independently selected from H, optionally substituted  $C_{1-22}$  alkyl and an optionally substituted  $C_{6-25}$  aryl group.

In one embodiment of the present invention,  $Q_1$  and/or  $Q_2$  does not contain a ligating atom or group and is selected from H, optionally substituted  $C_{1-22}$  alkyl and optionally substituted  $C_{6-25}$  aryl group, where the optional substituents are selected from  $C_{1-10}$  alkyl and  $C_{6-14}$  aryl. Preferably,  $Q_1$  and/or  $Q_2$  is selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl. More preferably,  $Q_1$  and/or  $Q_2$  is selected from H,  $C_{1-5}$  alkyl,  $C_{6-10}$  aryl and the benzyl group. Most preferred is when  $Q_1$  and/or  $Q_2$  is selected from H,  $C_{1-5}$  alkyl, benzyl and phenyl.

In another embodiment,  $Q_1$  and/or  $Q_2$  contains a group that can act as a ligating atom or group, or contains a polar functional group, which may further increase the solubility of the compound.  $Q_1$  and  $Q_2$  are each independently selected from H, optionally substituted  $C_{1-22}$  alkyl and optionally substituted  $C_{6-25}$  aryl group, where the optional substituents are selected from those provided in the list below. Preferably,  $Q_1$  and/or  $Q_2$  is selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl. More preferably,  $Q_1$  and/or  $Q_2$

is selected from H, C<sub>1-5</sub> alkyl and C<sub>6-10</sub> aryl.

In this embodiment, where Q<sub>1</sub> and/or Q<sub>2</sub> is a group that may be optionally substituted, it is preferred that the optional substituent is selected from  $\alpha$ -amino acid group, hydroxy, ether, ester, oxo, acyloxy, amino, amido and acylamido. More preferably, the optional substituent is selected from  $\alpha$ -amino acid group, hydroxy, ester and C<sub>1-7</sub> alkylamino. Most preferred is when the optional substituent is hydroxy.

In the embodiment where R<sup>1</sup> is a -[Alk]<sub>n</sub>-O-C(O)-Q and n = 1, it is preferred that Q<sub>1</sub> is selected from H, substituted C<sub>1-22</sub> alkyl and optionally substituted C<sub>6-25</sub> aryl group, where the preferred substituents are the same as those listed for the previous embodiment. More preferably, Q<sub>1</sub> is selected from H, substituted C<sub>6-22</sub> alkyl and optionally substituted C<sub>6-14</sub> aryl group. More particularly, Q<sub>1</sub> is selected from H and optionally substituted C<sub>6-10</sub> aryl group.

In yet another embodiment, R<sup>1</sup> is -[Alk]<sub>n</sub>-C(O)-O-Q<sub>1</sub> and n is 0 so that the carbonyl group is directly attached to the ring of the Cp group. In this embodiment, Q<sub>1</sub> is selected from H, optionally substituted C<sub>1-22</sub> alkyl and an optionally substituted C<sub>6-25</sub> aryl group. Preferably, Q<sub>1</sub> is H, C<sub>1-22</sub> alkyl and C<sub>6-25</sub> aryl. More preferably, Q<sub>1</sub> is H or C<sub>1-7</sub> alkyl. Most preferred is when Q<sub>1</sub> is H or methyl.

An embodiment of the present aspect of the invention, as described above, may be combined with another embodiment of the first aspect of the invention.

Organometallic compounds having a nitrosyl ligand coordinated directly to the transition metal centre, and pharmaceutical compositions containing such compounds, are excluded from the present invention.

The pharmaceutical compositions of the present invention typically comprise a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art.

Such materials should be non-toxic and should not interfere unduly with the efficacy of the active ingredient.

The precise nature of the carrier or other material may depend on the route of administration, e. g. oral, intravenous, transdermal, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal, or suppository routes.

5           Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may include a solid carrier such as gelatin or an adjuvant or a slow-release polymer. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum,  
10           animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. Pharmaceutically acceptable amounts of other solvents may also be included, in  
15           particular where they are required for dissolving the particular metal carbonyl compound contained in the composition.

          For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient  
20           will typically be in the form of a parenterally acceptable solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection,  
25           Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required. Delivery systems for needle-free injection are also known, and compositions for use with such systems may be prepared accordingly.

30           Administration is preferably in a prophylactically effective amount or a therapeutically effective amount (as the case may be, although prophylaxis may be considered therapy), this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of  
35           administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e. g. decisions

on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners.

Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.

When formulating pharmaceutical compositions according to the present invention, the toxicity of the active ingredient and/or the solvent must be considered.

The balance between medical benefit and toxicity should be taken into account. The dosages and formulations of the compositions will typically be determined so that the medical benefit provided outweighs any risks due to the toxicity of the constituents.

A second aspect of the present invention is compound represented by the formula (III)

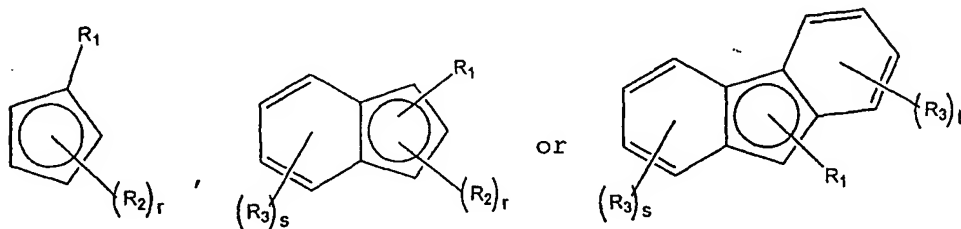


wherein

Y is a counteranion;

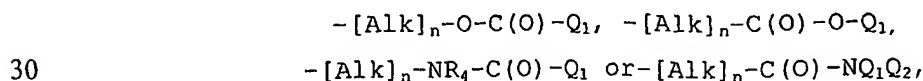
q is the charge of Y and is selected from 1, 2 or 3;

Cp is selected from:



where r, s and t are each independently selected from 1, 2, 3 or 4; and

R<sub>1</sub> is either:



n is 0 or 1;

Alk is a C<sub>1-28</sub> alkylene group;

Q<sub>1</sub> and Q<sub>2</sub> are each independently selected from H, optionally substituted C<sub>1-22</sub> alkyl and an optionally substituted C<sub>6-25</sub> aryl group;

each R<sub>2</sub> is independently selected from R<sub>1</sub>, H, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy, halide, formyl, C<sub>1-7</sub> alkylacyl and C<sub>6-20</sub> arylacyl;

R<sub>4</sub> is selected from H, C<sub>1-22</sub> alkyl and C<sub>6-25</sub> aryl;

each R<sub>3</sub> is independently selected from H, hydroxy, nitro, cyano, halide, sulfhydryl, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy, formyl, C<sub>1-7</sub> alkylacyl, C<sub>6-20</sub> arylacyl, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, carboxylic acid (-C(=O)OH), ester (-C(=O)OR<sup>5</sup>), acyloxy (-OC(=O)R<sup>5</sup>), amido (-C(=O)NR<sup>5</sup>R<sup>6</sup>), acylamido (-NR<sup>5</sup>C(=O)R<sup>6</sup>) and amino (-NR<sup>5</sup>R<sup>6</sup>); and

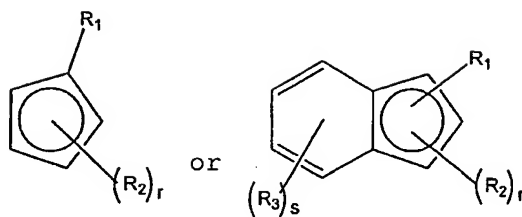
R<sup>5</sup> and R<sup>6</sup> are independently selected from H, C<sub>1-7</sub> alkyl and C<sub>6-20</sub> aryl.

In the second aspect of the invention, it is preferred that when the Cp group is indenyl or fluorenyl, the aryl ring substituent R<sub>3</sub> is selected from H, hydroxy, nitro, cyano, halide, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy and amino (-NR<sup>5</sup>R<sup>6</sup>). More preferably, R<sub>3</sub> is H, halide, C<sub>1-22</sub> alkyl and C<sub>6-25</sub> aryl. In particular, R<sub>3</sub> is H, methyl, ethyl or phenyl. Most particularly, R<sub>3</sub> is H.

When R<sub>3</sub> is not H, it is preferred that there are 1, 2 or 3 R<sub>3</sub> aryl ring substituents. More preferred are indenyl or fluorenyl ligands where there are a total of 1 or 2 R<sub>3</sub> aryl ring substituents.

Compounds according to the second aspect of the invention, preferably have a Cp group that is the cyclopentadienyl ligand or indenyl ligand





More preferably, Cp is the cyclopentadienyl ligand shown above. When Cp is the cyclopentadienyl ligand, the ring preferably contains one or four  $R_2$  substituents i.e.  $r = 1$  or 4, but more preferably  $r = 1$ .

The second substituent  $R_2$  may be independently selected from any of the groups for  $R_1$ . It is preferable that if  $R_2$  is to be independently selected from a group for  $R_1$ , that  $R_2$  and  $R_1$  are identical. If  $R_2$  is not selected from the groups defined for  $R_1$ , then it is preferred that  $R_2$  is selected from H,  $C_{1-22}$  alkyl and  $C_{9-25}$  aryl. Most preferably  $R_2$  is H or methyl, more particularly H.

In the present aspect of the invention,  $R_1$  is preferably  $-[Alk]_n-O-C(O)-Q_1$  or  $-[Alk]_n-C(O)-O-Q_1$ . Most preferred is when  $R_1$  is  $-[Alk]_n-C(O)-O-Q_1$ .

In one embodiment,  $R_1$  is  $-[Alk]_n-O-C(O)-Q_1$  or  $-[Alk]_n-C(O)-O-Q_1$ , more particularly  $-[Alk]_n-C(O)-O-Q_1$ , and  $n$  is 0. In this embodiment,  $Q_1$  is preferably selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl. In particular, the optional substituent is selected from  $C_{1-10}$  alkyl,  $C_{6-14}$  aryl,  $\alpha$ -amino acid group, hydroxy, ether, ester, oxo, acyloxy, amino, amido and acylamido. More preferably, the optional substituent is selected from  $\alpha$ -amino acid group, hydroxy, ester and  $C_{1-7}$  alkylamino. Most preferred is when the optional substituent is hydroxy. The most preferred groups for  $Q_1$  in this embodiment are  $C_{1-10}$  alkyl and  $C_{1-10}$  hydroxyalkyl, particularly methyl, ethyl and hydroxyethyl.

In an alternative embodiment of the second aspect,  $R_1$  is  $-[Alk]_n-O-C(O)-Q_1$  or  $-[Alk]_n-C(O)-O-Q_1$ , more particularly  $-[Alk]_n-C(O)-O-Q_1$ , and  $n$  is 1. "Alk" is preferably linear or

branched saturated C<sub>1-10</sub> alkylene group, which excludes the subclasses alkenylene, alkynylene and cycloalkylene. It is further preferred that "Alk" is a linear or unbranched saturated C<sub>1-6</sub> alkylene group or more preferably a C<sub>1-5</sub> alkylene group. Most preferred is when "Alk" is a linear saturated C<sub>1-4</sub> alkylene group, more particularly C<sub>1</sub> or C<sub>2</sub> alkylene. Preferably, Q<sub>1</sub> is selected from H, optionally substituted C<sub>1-10</sub> alkyl and optionally substituted C<sub>6-14</sub> aryl. More preferably, Q<sub>1</sub> is selected from H, C<sub>1-5</sub> alkyl, C<sub>6-10</sub> aryl and the benzyl group. Most preferred is when Q<sub>1</sub> is selected from H, C<sub>1-5</sub> alkyl, benzyl and phenyl. Preferred optional substituents are as listed for the previous embodiment. The counteranion Y may be selected from the list of counteranions given above for the first aspect of the invention. Preferably, the counteranion Y has a charge q of -1, such as when Y is a halide, borate or is hexafluorophosphate. Most preferred is when Y is Cl<sup>-</sup>, BF<sub>4</sub><sup>-</sup> or PF<sub>6</sub><sup>-</sup>.

A third aspect of the invention is a method of introducing CO to a mammal comprising the step of administering a pharmaceutical composition or compound according to the present invention. The method of introducing CO is for treatment of hypertension, such as acute, pulmonary and chronic hypertension, radiation damage, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction and adult respiratory distress syndrome.

The data presented herein is an extension of the work presented in WO 02/092075 and WO 2004/045598. Based on the work presented in these documents, it is preferred that the method of the present invention is for the treatment of hypertension, such as acute, pulmonary and chronic hypertension, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis,

hyperoxia-induced injury, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis and adult respiratory distress syndrome. More preferred is a method for  
5 the treatment of hypertension, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis, post-ischemic organ damage, myocardial infarction and sepsis. Even more preferred is a method for the treatment of hypertension, post-ischemic organ damage and myocardial  
10 infarction.

The present aspect of the invention also includes a method of treatment of an extracorporeal or isolated organ, comprising contacting the organ with a pharmaceutical composition according to the present invention. The metal  
15 carbonyl makes available carbon monoxide (CO) to limit post-ischemic damage. The organ treated in the method of the invention is an organ which is isolated from the blood supply. The organ may be extracorporeal e.g. a donated organ outside of the donor's body, or it may be isolated in the sense that  
20 it is in a patient's body and isolated from the blood supply for surgical purposes.

The organ may be, for example, a circulatory organ, respiratory organ, urinary organ, digestive organ, reproductive organ, neurological organ, muscle or skin flap or  
25 an artificial organ containing viable cells.

Most preferably, the organ is a heart, lung, kidney or liver. The contacting with the compositions containing metal carbonyl can be achieved by any method that exposes the organ to the composition e. g. bathing or pumping. Preferably, an  
30 isolated organ which is attached to the body, i.e. a bypassed organ, is perfused with the composition. An organ which is extracorporeal is preferably bathed in the composition.

In WO 02/092075 and WO 2004/045598 some of the present inventors demonstrated that metal carbonyl compounds can be  
35 used in the treatment of particular diseases. Thus, by extension, the present invention also provides the use of a

metal carbonyl compound as herein described in the manufacture of a medicament for delivering CO to a physiological target, particularly a mammal, to provide a physiological effect, e.g. for stimulating neurotransmission or vasodilation, or for  
5 treatment of any of hypertension, such as acute, pulmonary and chronic hypertension, radiation damage, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, arteriosclerosis, post-ischemic  
10 organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction and adult respiratory distress syndrome. Such medicaments may be adapted for administration by an oral, intravenous, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal or  
15 suppository route. Preferably the present invention excludes delivery of a metal carbonyl or a decomposition product thereof to an organism through the skin or mucosa.

More preferably, the use of a metal carbonyl compound as described herein is in the manufacture of a medicament for the  
20 treatment of hypertension, such as acute, pulmonary and chronic hypertension, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis, hyperoxia-induced injury, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage,  
25 myocardial infarction, angina, haemorrhagic shock, sepsis and adult respiratory distress syndrome. More preferred is a medicament for the treatment of hypertension, endotoxic shock, inflammation, inflammatory-related diseases such as asthma and rheumatoid arthritis, post-ischemic organ damage, myocardial  
30 infarction and sepsis. Even more preferred is a medicament for the treatment of hypertension, post-ischemic organ damage and myocardial infarction.

The invention further provides use of the metal carbonyls here described in treatment, e.g. by perfusion, of a viable  
35 mammalian organ extracorporeally, e.g. during storage and/or transport of an organ for transplant surgery. For this

purpose, the metal carbonyl is in dissolved form, preferably in an aqueous solution. The viable organ may be any tissue containing living cells, such as a heart, a kidney, a liver, a skin or muscle flap, etc.

5       A fourth aspect of the invention is a kit for producing a pharmaceutical solution. The kit comprises a compound as described herein and a pharmaceutically acceptable solvent. Some of the compounds described herein release CO upon dissolution. Storage of such CORMs in solution is thus  
10 impractical because the CORM will decompose or deactivate and will be unable to deliver CO to the physiological target. It is preferred that such CORMs are prepared using the kit according to the present invention immediately before administration to a human or mammalian patient.

15

#### Definitions

The term "physiological fluid", as used herein, pertains to fluid suitable for pharmaceutical administration to a physiological system, such as water or a saline solution, or  
20 to a fluid already present in a physiological system, such as blood plasma or blood.

The term "counteranion", as used herein, pertains to an atom or group having a formal negative charge that is present to  
25 balance the charge of the organometallic cation. The term encompasses anions which are known to be suitable within the art as counteranions for organometallic complexes, such as  $\text{BF}_4^-$ ,  $\text{PF}_6^-$  etc. The counteranion may be the conjugate base of a strong acid. Examples of counteranions that are a conjugate  
30 base of a strong acid are  $\text{Cl}^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{F}^-$ ,  $\text{ClO}_4^-$  etc. The counteranion may also be the conjugation base of a weak or organic acid, such as  $\text{CH}_3\text{COO}^-$  etc. The counteranion may have a charge greater than one, such as in  $\text{SO}_4^{2-}$ ,

It is preferred that the counteranion does not act as a  
35 nucleophile toward the cationic organometallic complex.

The acronyms OTs, OBs, OMs and OTf represent the anions

tosylate, brosylate, mesylate and triflate as is commonly known within the art.

#### Alkylene

5 Alkylene: The term "alkylene", as used herein, pertains to a bidentate moiety obtained by removing two hydrogen atoms, either both from the same carbon atom, or one from each of two different carbon atoms, of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may  
10 be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkylene" includes the sub-classes alkenylene, alkynylene, cycloalkylene, etc., discussed below.

In this context, the prefixes (e.g., C<sub>1-4</sub>, C<sub>1-7</sub>, C<sub>1-20</sub>, C<sub>2-7</sub>,  
15 C<sub>3-7</sub>, etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term "C<sub>1-4</sub>alkylene," as used herein, pertains to an alkylene group having from 1 to 4 carbon atoms. Examples of groups of alkylene groups include C<sub>1-4</sub>alkylene ("lower alkylene"), C<sub>1-7</sub>alkylene, and C<sub>1-20</sub>alkylene.

20 Examples of linear saturated C<sub>1-7</sub>alkylene groups include, but are not limited to, -(CH<sub>2</sub>)<sub>n</sub>- where n is an integer from 1 to 7, for example, -CH<sub>2</sub>- (methylene), -CH<sub>2</sub>CH<sub>2</sub>- (ethylene), -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- (propylene), and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>- (butylene).

Examples of branched saturated C<sub>1-7</sub>alkylene groups  
25 include, but are not limited to, -CH(CH<sub>3</sub>)-, -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>2</sub>CH<sub>3</sub>)-, -CH(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>-, and -CH<sub>2</sub>CH(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>-.

Examples of linear partially unsaturated C<sub>1-7</sub>alkylene  
30 groups include, but is not limited to, -CH=CH- (vinylene), -CH=CH-CH<sub>2</sub>-, -CH<sub>2</sub>-CH=CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH=CH-, -CH=CH-CH=CH-CH<sub>2</sub>-, -CH=CH-CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-, -CH=CH-CH<sub>2</sub>-CH=CH-, and -CH=CH-CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-.

Examples of branched partially unsaturated C<sub>1-7</sub>alkylene  
35 groups include, but is not limited to, -C(CH<sub>3</sub>)=CH-, -C(CH<sub>3</sub>)=CH-CH<sub>2</sub>-, and -CH=CH-CH(CH<sub>3</sub>)-.

Examples of alicyclic saturated C<sub>1-7</sub>alkylene groups include, but are not limited to, cyclopentylene (e.g. cyclopent-1,3-ylene), and cyclohexylene (e.g. cyclohex-1,4-ylene).

5        Examples of alicyclic partially unsaturated C<sub>1-7</sub>alkylene groups include, but are not limited to, cyclopentenylene (e.g. 4-cyclopenten-1,3-ylene), cyclohexenylene (e.g. 2-cyclohexen-1,4-ylene; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene).

10

The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

15        The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond. Compounds and/or groups may be partially unsaturated or fully unsaturated.

20        Alkyl: The term "alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 20 carbon atoms (unless otherwise specified), which may be aliphatic or alicyclic, and which may be saturated or  
25        unsaturated (e.g., partially unsaturated, fully unsaturated). Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, cycloalkylenyl, cylcoalkynyl, etc., as discussed below. Preferably, the term "alkyl" includes only the sub-class cycloalkyl. More preferably, "alkyl" does not  
30        include the sub-classes alkenyl, alkynyl, cycloalkyl, cycloalkylenyl and cylcoalkynyl.

          In the context of alkyl groups, the prefixes (e.g. C<sub>1-4</sub>, C<sub>1-7</sub>, C<sub>1-20</sub>, C<sub>2-7</sub>, C<sub>3-7</sub> etc.) denote the number of carbon atoms, or range of number of carbon atoms. For example, the term  
35        "C<sub>1-4</sub>alkyl," as used herein, pertains to an alkyl group having from 1 to 4 carbon atoms. Examples of groups of alkyl groups

include C<sub>1-4</sub>alkyl, C<sub>1-7</sub>alkyl, and C<sub>1-20</sub>alkyl. Note that the first prefix may vary according to other limitations; for example, for unsaturated alkyl groups, the first prefix must be at least 2; for cyclic and branched alkyl groups, the first prefix must be at least 3; etc.

Examples of (unsubstituted) saturated alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), propyl (C<sub>3</sub>), butyl (C<sub>4</sub>), pentyl (C<sub>5</sub>), hexyl (C<sub>6</sub>), and heptyl (C<sub>7</sub>).

Examples of (unsubstituted) saturated linear alkyl groups include, but are not limited to, methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), n-propyl (C<sub>3</sub>), n-butyl (C<sub>4</sub>), n-pentyl (amyl) (C<sub>5</sub>), n-hexyl (C<sub>6</sub>), and n-heptyl (C<sub>7</sub>).

Examples of (unsubstituted) saturated branched alkyl groups include iso-propyl (C<sub>3</sub>), iso-butyl (C<sub>4</sub>), sec-butyl (C<sub>4</sub>), tert-butyl (C<sub>4</sub>), iso-pentyl (C<sub>5</sub>), and neo-pentyl (C<sub>5</sub>).

Alkenyl: The term "alkenyl," as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.

Examples of groups of alkenyl groups include C<sub>2-4</sub>alkenyl, C<sub>2-7</sub>alkenyl, C<sub>2-20</sub>alkenyl.

Examples of (unsubstituted) unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, -CH=CH<sub>2</sub>), 1-propenyl (-CH=CH-CH<sub>3</sub>), 2-propenyl (allyl, -CH=CH-CH<sub>2</sub>), isopropenyl (1-methylvinyl, -C(CH<sub>3</sub>)=CH<sub>2</sub>), butenyl (C<sub>4</sub>), pentenyl (C<sub>5</sub>), and hexenyl (C<sub>6</sub>).

Alkynyl: The term "alkynyl," as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds.

Examples of groups of alkynyl groups include C<sub>2-4</sub>alkynyl, C<sub>2-7</sub>alkynyl, C<sub>2-20</sub>alkynyl.

Examples of (unsubstituted) unsaturated alkynyl groups include, but are not limited to, ethynyl (ethynyl, -C≡CH) and 2-propynyl (propargyl, -CH<sub>2</sub>-C≡CH).

Cycloalkyl: The term "cycloalkyl," as used herein, pertains



to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a carbocyclic ring of a carbocyclic compound, which carbocyclic ring may be saturated or  
5   unsaturated (e.g., partially unsaturated, fully unsaturated), which moiety has from 3 to 20 carbon atoms (unless otherwise specified), including from 3 to 20 ring atoms. Thus, the term "cycloalkyl" includes the sub-classes cycloalkenyl and cycloalkynyl. Preferably, each ring has from 3 to 7 ring  
10   atoms. Examples of groups of cycloalkyl groups include C<sub>3-20</sub>cycloalkyl, C<sub>3-15</sub>cycloalkyl, C<sub>3-10</sub>cycloalkyl, C<sub>3-7</sub>cycloalkyl.

Examples of cycloalkyl groups include, but are not limited to, those derived from:

saturated monocyclic hydrocarbon compounds:  
15   cyclopropane (C<sub>3</sub>), cyclobutane (C<sub>4</sub>), cyclopentane (C<sub>5</sub>), cyclohexane (C<sub>6</sub>), cycloheptane (C<sub>7</sub>), methylcyclopropane (C<sub>4</sub>), dimethylcyclopropane (C<sub>5</sub>);

unsaturated monocyclic hydrocarbon compounds:  
cyclopropene (C<sub>3</sub>), cyclobutene (C<sub>4</sub>), cyclopentene (C<sub>5</sub>),  
20   cyclohexene (C<sub>6</sub>), methylcyclopropene (C<sub>4</sub>), dimethylcyclopropene (C<sub>5</sub>), methylcyclobutene (C<sub>5</sub>);

saturated polycyclic hydrocarbon compounds:  
thujane (C<sub>10</sub>), carane (C<sub>10</sub>), pinane (C<sub>10</sub>), bornane (C<sub>10</sub>),  
norcarane (C<sub>7</sub>), norpinane (C<sub>7</sub>), norbornane (C<sub>7</sub>);

25   unsaturated polycyclic hydrocarbon compounds:  
camphene (C<sub>10</sub>), limonene (C<sub>10</sub>), pinene (C<sub>10</sub>).

Aryl: The term "aryl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an  
30   aromatic ring atom of an aromatic compound, which moiety has from 3 to 20 ring atoms (unless otherwise specified). Preferably, each ring has from 5 to 7 ring atoms.

In this context, the prefixes (e.g., C<sub>3-20</sub>, C<sub>5-7</sub>, C<sub>5-6</sub>, etc.) denote the number of ring atoms, or range of number of ring  
35   atoms, whether carbon atoms or heteroatoms. For example, the term "C<sub>5-6</sub>aryl," as used herein, pertains to an aryl group

having 5 or 6 ring atoms. Examples of groups of aryl groups include C<sub>3-20</sub>aryl, C<sub>5-20</sub>aryl, C<sub>5-15</sub>aryl, C<sub>5-12</sub>aryl and C<sub>5-10</sub>aryl.

The ring atoms may be all carbon atoms, as in "carboaryl groups." Examples of carboaryl groups include C<sub>3-20</sub>carboaryl, C<sub>5-20</sub>carboaryl, C<sub>5-15</sub>carboaryl, C<sub>5-12</sub>carboaryl and C<sub>5-10</sub>carboaryl.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C<sub>6</sub>), naphthalene (C<sub>10</sub>), azulene (C<sub>10</sub>), anthracene (C<sub>14</sub>), phenanthrene (C<sub>14</sub>), naphthacene (C<sub>18</sub>), and pyrene (C<sub>16</sub>).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indane (e.g. 2,3-dihydro-1H-indene) (C<sub>9</sub>), indene (C<sub>9</sub>), isoindene (C<sub>9</sub>), tetraline (1,2,3,4-tetrahydronaphthalene) (C<sub>10</sub>), acenaphthene (C<sub>12</sub>), fluorene (C<sub>13</sub>), phenalene (C<sub>13</sub>), acephenanthrene (C<sub>15</sub>), and aceanthrene (C<sub>16</sub>).

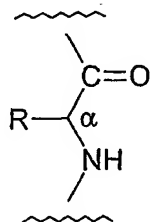
#### *Optional Substituents*

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known. Definitions for substituents are provided in the list below.

In formula (I) above, the groups Q<sub>1</sub>, Q<sub>2</sub> and/or R<sub>3</sub> may refer to a chemical moiety that may itself be optionally substituted with one or more groups selected from the additional substituents listed below.

$\alpha$ -Amino Acid Group: The term " $\alpha$ -amino acid group," as used herein, pertains to a group having the structure shown below:



which corresponds to an  $\alpha$ -amino acid of the following formula  
 5  $RC^{\alpha}H(NH_2)COOH$ . The  $\alpha$ -amino acid group may covalently bond as  
 an optional substituent by its amino nitrogen atom, by its  
 carbonyl carbon atom, both as shown in the diagram above, or  
 by its carboxylate oxygen atom. The remaining bond to the  
 carbonyl carbon atom or to the amino nitrogen atom may bond to  
 10 another  $\alpha$ -amino acid group to form a peptide chain.  
 Preferably, the peptide chain does not exceed five  $\alpha$ -amino  
 acid groups in length.

If the  $\alpha$ -amino acid group is bonded by the carbonyl  
 carbon atom or carboxylate oxygen atom, then group attached to  
 15 the amino nitrogen atom may be selected from H,  $C_{1-22}$  alkyl,  
 $C_{6-14}$  aryl,  $C_{1-22}$  alkoxy carbonyl and  $C_{6-14}$  aryloxy carbonyl.  
 Alternatively, if the  $\alpha$ -amino acid group is bonded by the  
 amino nitrogen atom, then the group bonded to the carbonyl  
 carbon atom may be selected from H,  $C_{1-22}$  alkyl,  $C_{6-14}$  aryl,  $C_{1-22}$   
 20 alkoxy and  $C_{6-14}$  aryloxy.

Examples of  $\alpha$ -amino acids include both natural amino  
 acids and non-natural amino acids. The natural amino acids  
 include: those with nonpolar (hydrophobic) R groups: alanine,  
 Ala, A; isoleucine, Ile, I; leucine, Leu, L; methionine, Met,  
 25 M; phenylalanine, Phe, F; proline, Pro, P; tryptophan, Trp, W;  
 and valine, Val, V; those with polar but uncharged R groups:  
 asparagine, Asn, N; cysteine, Cys, C; glutamine, Gln, Q;  
 glycine, Gly, G; serine, Ser, S; threonine, Thr, T; and  
 tyrosine, Tyr, Y; those with (potentially) positively charged  
 30 R groups: arginine, Arg, R; histidine, His, H; and lysine,  
 Lys, K; and those with (potentially) negatively charged R  
 groups: aspartic acid, Asp, D; glutamic acid, Glu, E.

An example of an  $\alpha$ -amino acid group, but is not limited to, is  $-\text{O}-\text{CO}-\text{CHMeNHC}(\text{O})\text{OC}(\text{CH}_3)_3$ , which is a Boc protected alanine  $\alpha$ -amino acid group.

- 5     Halo:  $-\text{F}$ ,  $-\text{Cl}$ ,  $-\text{Br}$ , and  $-\text{I}$ .  
Hydroxy:  $-\text{OH}$ .  
Nitro:  $-\text{NO}_2$ .  
Cyano (nitrile, carbonitrile):  $-\text{CN}$ .  
Ether:  $-\text{OR}$ , wherein R is an ether substituent, for example, a  
10      $\text{C}_{1-7}$  alkyl group (also referred to as a  $\text{C}_{1-7}$  alkoxy group, discussed below), or a  $\text{C}_{5-20}$  aryl group (also referred to as a  $\text{C}_{5-20}$  aryloxy group), preferably a  $\text{C}_{1-7}$  alkyl group.  
Alkoxy:  $-\text{OR}$ , wherein R is an alkyl group, for example, a  $\text{C}_{1-7}$  alkyl group. Examples of  $\text{C}_{1-7}$  alkoxy groups include, but are  
15     not limited to,  $-\text{OMe}$  (methoxy),  $-\text{OEt}$  (ethoxy),  $-\text{O}(\text{nPr})$  (n-propoxy),  $-\text{O}(\text{iPr})$  (isopropoxy),  $-\text{O}(\text{nBu})$  (n-butoxy),  $-\text{O}(\text{sBu})$  (sec-butoxy),  $-\text{O}(\text{iBu})$  (isobutoxy), and  $-\text{O}(\text{tBu})$  (tert-butoxy).  
Oxo (keto, -one):  $=\text{O}$ .  
Thione (thioketone):  $=\text{S}$ .  
20     Imino (imine):  $=\text{NR}^5$ , wherein  $\text{R}^5$  is an imino substituent, for example, hydrogen,  $\text{C}_{1-7}$  alkyl group, or a  $\text{C}_{5-20}$  aryl group, preferably hydrogen or a  $\text{C}_{1-7}$  alkyl group. Examples of ester groups include, but are not limited to,  $=\text{NH}$ ,  $=\text{NMe}$ ,  $=\text{NEt}$ , and  $=\text{NPh}$ .  
25     Formyl (carbaldehyde, carboxaldehyde):  $-\text{C}(=\text{O})\text{H}$ .  
Acyl (keto):  $-\text{C}(=\text{O})\text{R}^5$ , wherein  $\text{R}^5$  is an acyl substituent, for example, a  $\text{C}_{1-7}$  alkyl group (also referred to as  $\text{C}_{1-7}$  alkylacyl or  $\text{C}_{1-7}$  alkanoyl), or a  $\text{C}_{5-20}$  aryl group (also referred to as  $\text{C}_{5-20}$  arylacyl), preferably a  $\text{C}_{1-7}$  alkyl group. Examples of acyl  
30     groups include, but are not limited to,  $-\text{C}(=\text{O})\text{CH}_3$  (acetyl),  $-\text{C}(=\text{O})\text{CH}_2\text{CH}_3$  (propionyl),  $-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$  (t-butyryl), and  $-\text{C}(=\text{O})\text{Ph}$  (benzoyl, phenone).  
Carboxy (carboxylic acid):  $-\text{C}(=\text{O})\text{OH}$ .  
Thiocarboxy (thiocarboxylic acid):  $-\text{C}(=\text{S})\text{SH}$ .  
35     Thiocarboxy (thiocarboxylic acid):  $-\text{C}(=\text{O})\text{SH}$ .  
Thionocarboxy (thionocarboxylic acid):  $-\text{C}(=\text{S})\text{OH}$ .

Imidic acid:  $-C(=NH)OH$ .

Hydroxamic acid:  $-C(=NOH)OH$ .

Ester (carboxylate, carboxylic acid ester, oxycarbonyl):

5  $-C(=O)OR^5$ , wherein  $R^5$  is an ester substituent, for example, a  $C_{1-7}$  alkyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of ester groups include, but are not limited to,  $-C(=O)OCH_3$ ,  $-C(=O)OCH_2CH_3$ ,  $-C(=O)OC(CH_3)_3$ , and  $-C(=O)OPh$ .

10 Acyloxy (reverse ester):  $-OC(=O)R^5$ , wherein  $R^5$  is an acyloxy substituent, for example, a  $C_{1-7}$  alkyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of acyloxy groups include, but are not limited to,  $-OC(=O)CH_3$  (acetoxy),  $-OC(=O)CH_2CH_3$ ,  $-OC(=O)C(CH_3)_3$ ,  $-OC(=O)Ph$ , and  $-OC(=O)CH_2Ph$ .

15 Oxy-carboxyloxy:  $-OC(=O)OR^5$ , wherein  $R^5$  is an ester substituent, for example, a  $C_{1-7}$  alkyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Examples of ester groups include, but are not limited to,  $-OC(=O)OCH_3$ ,  $-OC(=O)OCH_2CH_3$ ,  $-OC(=O)OC(CH_3)_3$ , and  $-OC(=O)OPh$ .

Amino:  $-NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently amino substituents, for example, hydrogen, a  $C_{1-7}$  alkyl group (also referred to as  $C_{1-7}$  alkylamino or di- $C_{1-7}$  alkylamino), or a  $C_{5-20}$  aryl group, preferably H or a  $C_{1-7}$  alkyl group, or, in the case of a "cyclic" amino group,  $R^5$  and  $R^6$ , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be  
20 primary ( $-NH_2$ ), secondary ( $-NHR^5$ ), or tertiary ( $-NHR^5R^6$ ), and in cationic form, may be quaternary ( $-^+NR^5R^6R^7$ ). Examples of amino groups include, but are not limited to,  $-NH_2$ ,  $-NHCH_3$ ,  $-NHC(CH_3)_2$ ,  $-N(CH_3)_2$ ,  $-N(CH_2CH_3)_2$ , and  $-NHPh$ . Examples of cyclic amino groups include, but are not limited to, aziridino,  
25 azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.  
30

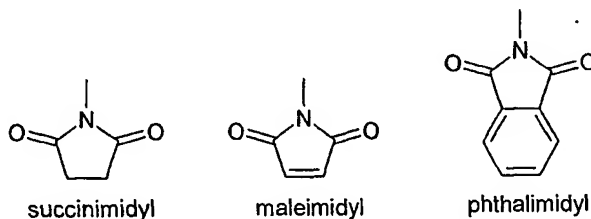
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide):

35  $-C(=O)NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to,  $-C(=O)NH_2$ ,  $-C(=O)NHCH_3$ ,  $-C(=O)N(CH_3)_2$ ,  $-C(=O)NHCH_2CH_3$ , and  $-C(=O)N(CH_2CH_3)_2$ , as well as

amido groups in which  $R^5$  and  $R^6$ , together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

- 5 Thioamido (thiocarbamyl):  $-C(=S)NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently amino substituents, as defined for amino groups.  
 Acylamido (acylamino):  $-NR^5C(=O)R^6$ , wherein  $R^5$  is an amide substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group, and  
 10  $R^6$  is an acyl substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group. Examples of acylamide groups include, but are not limited to,  $-NHC(=O)CH_3$ ,  $-NHC(=O)CH_2CH_3$ , and  $-NHC(=O)Ph$ .  $R^5$  and  $R^6$  may together form a cyclic  
 15 structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl.

20



25

Aminocarbonyloxy:  $-OC(=O)NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently amino substituents, as defined for amino groups. Examples of aminocarbonyloxy groups include, but are not limited to,  $-OC(=O)NH_2$ ,  $-OC(=O)NHMe$ ,  $-OC(=O)NMe_2$ , and  $-OC(=O)NEt_2$ .

30

Aminothiocabonylthiol:  $-SC(=S)NR^5R^6$ , wherein  $R^5$  and  $R^6$  are independently amino substituents, as defined for amino groups. Examples of aminocarbonyloxy groups include, but are not limited to,  $-SC(=S)NH_2$ ,  $-SC(=S)NHMe$ , and  $-SC(=S)NMe_2$ .

35

Ureido:  $-N(R^5)CONR^6R^7$  wherein  $R^6$  and  $R^7$  are independently amino substituents, as defined for amino groups, and  $R^5$  is a ureido substituent, for example, hydrogen, a  $C_{1-7}$  alkyl group, or a  $C_{5-20}$  aryl group, preferably hydrogen or a  $C_{1-7}$  alkyl group.

Guanidino:  $-NH-C(=NH)NH_2$ .

Imino:  $=NR$ , wherein  $R$  is an imino substituent, for example,

for example, hydrogen, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably H or a C<sub>1-7</sub> alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, and =NEt.

Amidine (amidino): -C(=NR)NR<sub>2</sub>, wherein each R is an amidine substituent, for example, hydrogen, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably H or a C<sub>1-7</sub> alkyl group.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C<sub>1-7</sub> alkyl group (also referred to as a C<sub>1-7</sub> alkylthio group), or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of C<sub>1-7</sub> alkylthio groups include, but are not limited to, -SCH<sub>3</sub> and -SCH<sub>2</sub>CH<sub>3</sub>.

Sulfine (sulfinyl, sulfoxide): -S(=O)R, wherein R is a sulfine substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfone (sulfonyl): -S(=O)<sub>2</sub>R, wherein R is a sulfone substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)<sub>2</sub>CH<sub>3</sub> (methanesulfonyl, mesyl), -S(=O)<sub>2</sub>CF<sub>3</sub> (triflyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (esyl), -S(=O)<sub>2</sub>C<sub>4</sub>F<sub>9</sub> (nonafllyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> (tresyl), -S(=O)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> (tauryl), -S(=O)<sub>2</sub>Ph (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-bromophenylsulfonyl (brosyl) and 4-nitrophenyl (nosyl).

Sulfinic acid (sulfinic): -S(=O)OH, -SO<sub>2</sub>H.

Sulfonic acid (sulfo): -S(=O)<sub>2</sub>OH, -SO<sub>3</sub>H.

Sulfinate (sulfinic acid ester): -S(=O)OR; wherein R is a sulfinate substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfonate (sulfonic acid ester): -S(=O)<sub>2</sub>OR, wherein R is a sulfonate substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfinyloxy: -OS(=O)R, wherein R is a sulfinyloxy substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfonyloxy: -OS(=O)<sub>2</sub>R, wherein R is a sulfonyloxy substituent,

for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfate: -OS(=O)<sub>2</sub>OR; wherein R is a sulfate substituent, for example, a C<sub>1-7</sub>alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide):

-S(=O)NR<sup>5</sup>R<sup>6</sup>, wherein R<sup>5</sup> and R<sup>6</sup> are independently amino substituents, as defined for amino groups.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide):

-S(=O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, wherein R<sup>5</sup> and R<sup>6</sup> are independently amino substituents, as defined for amino groups.

Sulfamino: -NR<sup>5</sup>S(=O)<sub>2</sub>OH, wherein R<sup>5</sup> is an amino substituent, as defined for amino groups.

Sulfonamino: -NR<sup>5</sup>S(=O)<sub>2</sub>R, wherein R<sup>5</sup> is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub>alkyl group.

Sulfinamino: -NR<sup>5</sup>S(=O)R, wherein R<sup>5</sup> is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group, preferably a C<sub>1-7</sub> alkyl group.

Phospho: -P(=O)<sub>2</sub>.

Phosphinyl (phosphine oxide): -P(=O)R<sub>2</sub>, wherein R is a phosphinyl substituent, for example, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group.

Phosphonic acid (phosphono): -P(=O)(OH)<sub>2</sub>.

Phosphonate (phosphono ester): -P(=O)(OR)<sub>2</sub>, where R is a phosphonate substituent, for example, -H, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group.

Phosphoric acid (phosphonooxy): -OP(=O)(OH)<sub>2</sub>.

Phosphate (phosphonooxy ester): -OP(=O)(OR)<sub>2</sub>, where R is a phosphate substituent, for example, -H, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group.

Phosphorous acid: -OPH(=O)(OH).

Phosphite: -OP(OR)<sub>2</sub>, where R is a phosphite substituent, for example, -H, a C<sub>1-7</sub> alkyl group, or a C<sub>5-20</sub> aryl group.



Phosphoramidite:  $-\text{OP}(\text{OR}^5)-\text{NR}^6_2$ , where  $\text{R}^5$  and  $\text{R}^6$  are phosphoramidite substituents, for example,  $-\text{H}$ , a  $\text{C}_{1-7}$  alkyl group, or a  $\text{C}_{5-20}$  aryl group.

5 Phosphoramidate:  $-\text{OP}(=\text{O})(\text{OR}^5)-\text{NR}^6_2$ , where  $\text{R}^5$  and  $\text{R}^6$  are phosphoramidate substituents, for example,  $-\text{H}$ , a  $\text{C}_{1-7}$  alkyl group, or a  $\text{C}_{5-20}$  aryl group.

Siloxy (silyl ether):  $-\text{OSiR}_3$ , where  $\text{SiR}_3$  is a silyl group, as discussed above.

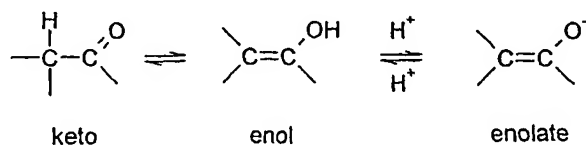
## 10 Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, stereoisomeric or tautomeric forms, and are herein collectively referred to as "isomers" (or "isomeric forms").

15 Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e. isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to  
20 a methoxy group,  $-\text{OCH}_3$ , is not to be construed as a reference to its structural isomer, a hydroxymethyl group,  $-\text{CH}_2\text{OH}$ .

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for  
25 example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.

30



Note that specifically included in the term "isomer" are  
35 compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including  $^1\text{H}$ ,  $^2\text{H}$  (D),

and  $^3\text{H}$  (T).

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly  
5 or partially) racemic and other mixtures thereof.

#### *Salts*

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for  
10 example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a  
15 functional group which may be anionic, such as an acidic group (e.g.,  $-\text{COOH}$  may be  $-\text{COO}^-$ ), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as  $\text{Na}^+$  and  $\text{K}^+$ , alkaline earth cations such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , and other  
20 cations such as  $\text{Al}^{3+}$ . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e.,  $\text{NH}_4^+$ ) and substituted ammonium ions (e.g.,  $\text{NH}_3\text{R}^+$ ,  $\text{NH}_2\text{R}_2^+$ ,  $\text{NHR}_3^+$ ,  $\text{NR}_4^+$ ).

Unless otherwise specified, a reference to a particular compound also include salt forms thereof.

25

#### *Solvates*

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to  
30 refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate.

Unless otherwise specified, a reference to a particular compound also include solvate forms thereof.

35

Throughout this application references to medical treatment

are intended to include both human and veterinary treatment, and references to pharmaceutical compositions are accordingly intended to encompass compositions for use in human or veterinary treatment.

5

#### Brief Description of the drawings

Experimental data illustrating the present invention will now be described by reference to the accompanying figures, in which:

10

Figure 1 is a table presenting CO release data and solubility data for some example compounds, which were proposed as being suitable as CO releasers to a physiological system in WO 03/066067.

15

Figure 2 is a table presenting data of solubility, CO release, cytotoxicity and anti-inflammatory action for some compounds according to the present invention, and also data of two comparative compounds (CORM-358 and CORM-360).

#### Embodiments of the invention and experimental data

20

##### **Detection of CO liberated from transition metal carbonyl complexes**

25

The release of CO from metal carbonyl complexes was assessed spectrophotometrically by measuring the conversion of deoxymyoglobin (deoxy-Mb) to carbonmonoxymyoglobin (MbCO). MbCO has a distinctive absorption spectrum between 500 and 600 nm, and changes at 540 nm were used to quantify the amount of CO liberated. Myoglobin solutions were prepared freshly by dissolving a known concentration of the protein in phosphate buffer, which was also made up to a known concentration and pH. Sodium dithionite (0.1 %) was added to convert myoglobin to deoxy-Mb prior to each reading. All the spectra were measured using a Helios  $\alpha$  spectrophotometer.

35

### Cytotoxicity

Cytotoxicity was measured in RAW264.7 macrophages incubated for 24 h with 10, 50 or 100  $\mu$ M of each compound. The loss in cell viability was measured using the Alamar Blue and LDH release assays as a percentage of control. In Table 2, \* indicates toxicity detected at 100  $\mu$ M; \*\* indicates toxicity detected at 50  $\mu$ M; \*\*\* indicates toxicity detected at 10  $\mu$ M; V indicates that cells were viable and no toxicity was detected up to 100  $\mu$ M.

### Anti-inflammatory action

The anti-inflammatory action was measured in RAW264.7 macrophages incubated for 24 h with 10, 50 or 100  $\mu$ M of each compound in the presence or absence of Lipopolysachharide (LPS) (1  $\mu$ g/ml). Nitrite was used as an indicator of inflammation. In Table 2, \* indicates a reduction in inflammation detected at 100  $\mu$ M; \*\* indicates a reduction in inflammation detected at 50  $\mu$ M; \*\*\* indicates a reduction in inflammation detected at 10  $\mu$ M; "None" indicates there was no effect of the compound on inflammation.

In Table 2, N.D.=not determined.

### Preparation of $C_5H_5COOMe$

A solution of LiCp was prepared by the addition of 156.3 ml (0.25 mol) of n-BuLi (1.6M in hexanes) to 20.65 ml (0.25 mol) of freshly cracked cyclopentadiene in 280 ml of dry THF at  $-78^\circ\text{C}$ , under argon. After complete addition, the system is allowed to warm slowly to room temperature and then stirred for a further hour. During this time a copious white precipitate is formed.

Following this, the system is again cooled to  $-78^\circ\text{C}$  (at which point the precipitate starts to redissolve) and 19.3 ml (0.25 mol) of methyl chloroformate is added dropwise. This results in complete disappearance of the white precipitate and

formation of a yellow/orange coloured solution. After warming to room temperature and then stirring for a further hour, a white precipitate is produced (LiCl).

500 ml of water is added and the two layers separated.  
5 The aqueous layer is washed with 2× 100 ml portions of ether, and then the combined organic extracts are washed with 5× 250 ml portions of water then 1× saturated brine. It is then dried (MgSO<sub>4</sub> at 0°C for 45 mins) and then the solvent removed on rotary evaporator to give a yellow oil. The yellow oil is used  
10 without further purification.

#### Reaction of C<sub>5</sub>H<sub>5</sub>COOMe with Fe(CO)<sub>5</sub> (10)

The product obtained from the above reaction was refluxed with 20 ml (0.15 mol) of Fe(CO)<sub>5</sub> in 110 ml of heptane/diglyme  
15 (10:1), under argon for 20 hrs. Following this, the system is cooled to -18°C overnight, and the resulting purple precipitate is collected on a sinter. It is washed with 2× portions of cold pentane.

The precipitate yields the product [Fe(Cp-COOMe)(CO)<sub>2</sub>]<sub>2</sub>  
20 which may be purified by column chromatography on silica, eluting with petrol to remove unreacted Fe(CO)<sub>5</sub> and then petrol/ether (1:1) to elute the product. Approximately 2.5 to 3 g of [Fe(Cp-COOMe)(CO)<sub>2</sub>]<sub>2</sub> was obtained using this method.

Alternatively, the crude [Fe(Cp-COOMe)(CO)<sub>2</sub>]<sub>2</sub> product may  
25 be purified by recrystallisation from DCM/hexane (following several hours under high vacuum to remove any traces of solvent and unreacted Fe(CO)<sub>5</sub>). This method gave higher yields and around 4 g of product was obtained in this way.

#### 30 Reaction of C<sub>5</sub>H<sub>5</sub>COOMe with Fe<sub>2</sub>(CO)<sub>9</sub> (11)

An alternative method for the synthesis of [Fe(Cp-COOMe)(CO)<sub>2</sub>]<sub>2</sub> involves a reaction with Fe<sub>2</sub>(CO)<sub>9</sub>.

C<sub>5</sub>H<sub>5</sub>COOMe, prepared from the above reaction, is refluxed

with 20 g (55.0 mmol) of  $\text{Fe}_2(\text{CO})_9$  in 200 ml of de-oxygenated heptane (argon purge), under argon for 24 hrs. After reflux, it is cooled to  $-18^\circ\text{C}$  overnight and a purple crystalline precipitate results, which may be collected on a sinter and washed with several portions of pentane. The heptane supernatant may be recycled, which may increase the yield. The yield typically varies from 4.5 to 6 g. (17.4 - 23.2% based on  $\text{Fe}_2(\text{CO})_9$ ). An advantage of this route is that recrystallisation is not required.

*Analytical data for  $[\text{Fe}(\text{Cp-COOMe})(\text{CO})_2]_2$*

I.R. ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}} = 2010.13, 1973.15 \text{ cm}^{-1}$  (terminal CO),  $1793.23 \text{ cm}^{-1}$  (bridging CO),  $1718.26 \text{ cm}^{-1}$  (C=O).

$^1\text{H-NMR}$  ( $d_6$ -acetone)  $\delta = 3.90$  (3H),  $5.17$  (2H),  $5.45$  (2H).

*Preparation of  $[\text{Fe}(\text{Cp-CO}_2\text{CH}_2\text{CH}_2\text{OH})(\text{CO})_2]_2$*

1.013 g (2.16 mmol) of  $[\text{Fe}(\text{Cp-COOMe})(\text{CO})_2]_2$  and 15 mg (0.375 mmol) of NaH (60% disp. in mineral oil) were stirred in 18 ml of ethylene glycol at  $55^\circ\text{C}$  overnight, under argon.

Following this, DCM and de-oxygenated water were added, and the two layers separated. The aqueous layer is washed with DCM and then the combined DCM extracts are washed with 3× portions of de-oxygenated water and 1× saturated brine. It was then dried ( $\text{MgSO}_4$ ) and the solvent removed on rotary evaporator. The resulting solid is washed with several portions of ether.

1.001 g of dark purple solid was produced in a yield of 87.5%. The sample may be recrystallised from DCM/hexane, which lowers the yield to around 62%.

*Analytical data for  $[\text{Fe}(\text{Cp-CO}_2\text{CH}_2\text{CH}_2\text{OH})(\text{CO})_2]_2$*

I.R. ( $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}} = 2012.13, 1975.15 \text{ cm}^{-1}$  (terminal CO),  $1785.23 \text{ cm}^{-1}$  (bridging CO),  $1718.26 \text{ cm}^{-1}$  (C=O).

$^1\text{H-NMR}$  ( $\text{CD}_2\text{Cl}_2$ )  $\delta = 3.97$  (2H),  $4.45$  (2H),  $5.03$  (2H),  $5.35$

(obscured by DCM peak) (2H).

**Preparation of  $[\text{Fe}(\text{Cp}-\text{CO}_2\text{CH}_2\text{CH}_2\text{OH})(\text{CO})_3][\text{PF}_6]$  {CORM-337} (12)**

500 mg (0.943 mmol) of  $[\text{Fe}(\text{Cp}-\text{CO}_2\text{CH}_2\text{CH}_2\text{OH})(\text{CO})_2]_2$  and 615 mg (1.86 mmol, 0.985 eq) of ferrocenium hexafluorophosphate were placed in a Schlenk tube under a CO atmosphere. 70 ml of a CO-saturated DCM/THF mixture (2:1) was then added and the system stirred for 2.5-3 days in the dark with periodic bubbling of CO through the solution.

Following this, some yellow precipitate had started to form and precipitation was completed by addition of ether (150 ml). After stirring for 10 mins the product was collected on a sinter, washed several times with ether, and then dried under vacuum.

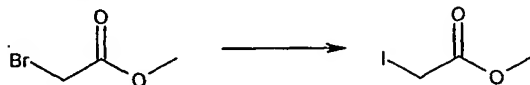
485 mg of a pale yellow solid was obtained. Yield was 59.7%.

**Analytical data for  $[\text{Fe}(\text{Cp}-\text{CO}_2\text{CH}_2\text{CH}_2\text{OH})(\text{CO})_3][\text{PF}_6]$**

I.R. (solid)  $\nu_{\text{max}} = 2134.4, 2102.1, 2077.6 \text{ cm}^{-1}$  (CO),  $1719.6 \text{ cm}^{-1}$  (C=O).

$^1\text{H-NMR}$  ( $\text{d}_6$ -acetone)  $\delta = 3.89$  (2H), 4.40 (2H), 6.20 (2H), 6.77 (2H).

**Preparation of Methyl Iodoacetate**



The following procedure was based on a modified literature method (14). A mixture of methyl bromoacetate (20.00 g, 12.40 mL, 130.74 mmol) and sodium iodide (25.10 g, 167.34 mmol, 1.28 equiv.) in acetone (90 mL) was stirred at room temperature for 15 hours and then heated at 50°C for 2 hours. The reaction mixture was then cooled to ambient temperature, filtered to remove sodium bromide and the solid was washed with diethyl ether (2 x 50 mL). The filtrate was concentrated in vacuo,

diluted with diethyl ether (100 mL) and the organic layer was washed with water (2 x 50 mL), brine (50 mL), dried (anhydrous sodium sulfate) and evaporated to give methyl iodoacetate (18.69 g, 93.46 mmol, 72%) as a dark red oil.

5.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.73 (3H, s,  $\text{OCH}_3$ ), 3.68 (2H, s,  $\text{ICH}_2$ ).

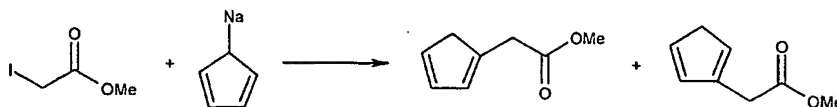
#### Preparation of Methyl 3-iodopropionate



10 Using the above modified Finkelstein procedure (14), methyl 3-iodopropionate (23.10 g, 107.94 mmol, 90%) was prepared from methyl 3-bromopropionate (20.00 g, 119.75 mmol) and sodium iodide (22.98 g, 153.28 mmol, 1.28 equiv.) in acetone (80 mL) as an orange oil.

15  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.71 (3H, s,  $\text{OCH}_3$ ), 3.31 (2H, s,  $J = 7.2$  Hz,  $\text{ICH}_2$ ), 2.97 (2H, s,  $J = 7.2$  Hz,  $\text{CH}_2\text{CO}_2$ ).

#### Preparation of Methyl Cyclopenta-1,3-dienylacetate and Methyl Cyclopenta-1,4-dienylacetate



20 The above compounds were prepared using a modified literature method (15, 16). A solution of methyl iodoacetate (18.50 g, 92.51 mmol) in anhydrous tetrahydrofuran (60 mL) was added dropwise to a 2.0 M solution of sodium cyclopentadienide (46.26 mL, 92.51 mmol) in tetrahydrofuran over 15 minutes

25 under nitrogen at  $-78^\circ\text{C}$ . The resulting reaction mixture was stirred for a further 3 hours at  $-78^\circ\text{C}$  and then warmed to room temperature, filtered and the resulting solid was washed with diethyl ether (200 mL). The combined organics were

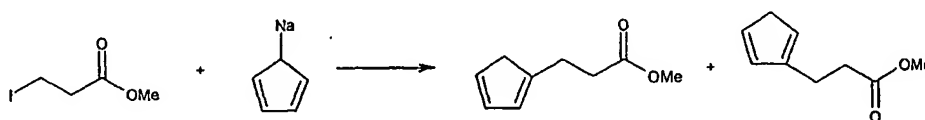
30 concentrated *in vacuo*. The crude oil was purified by flash chromatography on silica using 10% ethyl acetate in *iso*-hexane to afford methyl 3-cyclopenta-1,3-dienylacetate (1-alkylCp) and methyl 3-cyclopenta-1,4-dienylacetate (2-alkylCp) (2.37 g,



17.31 mmol, 19%) as yellow liquids in a approx. 1:1 ratio.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.53 (1H, m, cyclopentadiene CH),  
6.46 (2H, m, cyclopentadiene CH), 6.37 (2H, m, cyclopentadiene  
CH), 6.23 (1H, m, cyclopentadiene CH), 3.72 (3H, s, OCH<sub>3</sub>), 3.71  
5 (3H, s, OCH<sub>3</sub>), 3.47 (2H, m, alkyl CH<sub>2</sub>), 3.44 (2H, m, alkyl CH<sub>2</sub>),  
3.04 (2H, m, cycloalkyl CH<sub>2</sub>), 3.02 (2H, m, cycloalkyl CH<sub>2</sub>).

#### Preparation of Methyl 3-cyclopenta-1,3-dienylpropionate and Methyl 3-cyclopenta-1,4-dienylpropionate



10

The above compounds were prepared using a modified literature  
method (16). A 2.0 M solution of sodium cyclopentadienide in  
tetrahydrofuran (105.10 mL, 210.28 mmol) was added dropwise  
over 15 minutes to a stirred solution of methyl

15

3-iodopropionate (45.00 g, 210.28 mmol) in anhydrous diethyl  
ether (280 mL) and anhydrous tetrahydrofuran (200 mL) under  
nitrogen at -78°C. The resulting reaction mixture was stirred  
at -78°C for 2 hours and then stored at -20°C for a further 15  
hours. The resulting red suspension was quenched with 1 M

20

ammonium chloride solution (800 mL), and the organic phase was  
extracted with diethyl ether (5 x 400 mL). The combined  
organic layer was washed with 1 M ammonium chloride solution  
(2 x 500 mL) and dried (anhydrous sodium sulfate), filtered  
and concentrated *in vacuo*. The crude oil was purified by

25

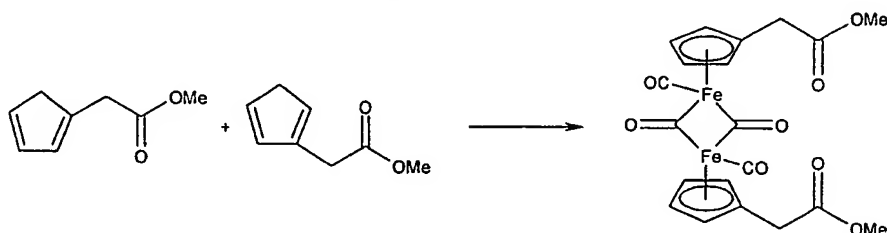
flash chromatography on silica using 5% ethyl acetate in iso-  
hexane to afford methyl 3-cyclopenta-1,3-dienylpropionate  
(1-alkylCp) and methyl 3-cyclopenta-1,4-dienylpropionate  
(2-alkylCp) (14.72 g, 96.72 mmol, 46%) as yellow liquids in a  
1.2:1 ratio.

30

Major isomer (1-alkylCp): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.40 (1H,  
m, Cp-H3, overlaps with xb), 6.25 (1H, m, Cp-H4), 6.02 (1H, m,  
Cp-H2), 3.66 (3H, s, OCH<sub>3</sub>), 2.93 (2H, dd, *J* = 3.7 and 1.9 Hz,  
Cp-H5), 2.71 (2H, m, CH<sub>2</sub>CO<sub>2</sub>, overlaps with xb), 2.55 (2H, m,  
CpCH<sub>2</sub>, overlaps with xb); Minor isomer (2-alkylCp): <sup>1</sup>H NMR (400

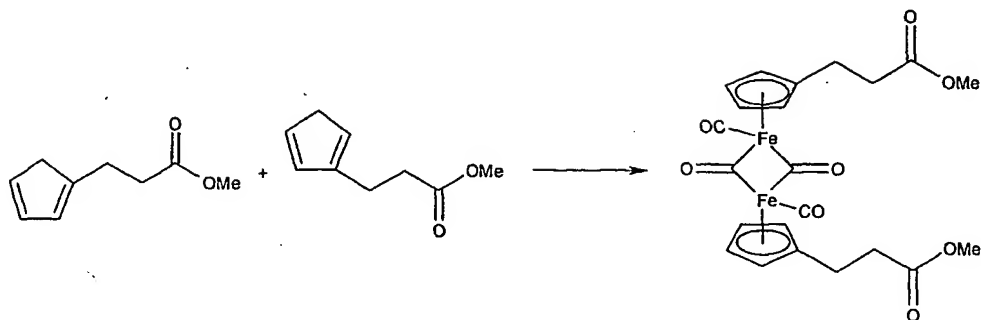
MHz, CDCl<sub>3</sub>) δ 6.40 (1H, m, Cp-H3, overlaps with xa), 6.39 (1H, m, Cp-H4, overlaps with xa), 6.16 (1H, m, Cp-H1), 3.66 (3H, s, OCH<sub>3</sub>), 2.88 (2H, dd, *J* = 2.9 and 1.5 Hz, Cp-H5), 2.71 (2H, m, CH<sub>2</sub>CO<sub>2</sub>, overlaps with xa), 2.55 (2H, m, CpCH<sub>2</sub>, overlaps with xa).

#### Preparation of [Fe(C<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>CO<sub>2</sub>Me)(CO)<sub>2</sub>]<sub>2</sub>



A mixture of methyl 3-cyclopenta-1,3-dienylacetate (1-alkylCp) and methyl 3-cyclopenta-1,4-dienylacetate (2-alkylCp) (2.00 g, 14.59 mmol) in degassed heptane (55 mL) was added to diiron nonacarbonyl (5.31 g, 14.59 mmol) under nitrogen at room temperature. The resulting reaction mixture was heated to reflux at 110°C and stirred for 18 hours, then cooled to ambient temperature during which precipitation of maroon-like crystals were observed. The solution was further cooled in the freezer for 1 hour and then the solution was filtered through a sinter funnel. The crystals collected were washed thoroughly with degassed hexane (4 x 50 mL). The crystals were dissolved in degassed dichloromethane (4 x 50 mL) and the solvent was concentrated *in vacuo* to yield the iron sandwich complex (2.67 g, 5.36 mmol, 30%) as maroon-like crystals.

IR (solid)  $\nu_{\max}$  cm<sup>-1</sup> 1979 (s, terminal CO), 1946 (s, terminal CO), 1759 (s, bridging C=O), 1737 (s, ester C=O); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>, room temperature) δ 4.76 (4H, s, 4 x cyclopentadiene CH), 4.69 (4H, s, 4 x cyclopentadiene CH), 3.74 (6H, s, 2 x OCH<sub>3</sub>), 3.56 (4H, s, 2 x alkyl CH<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>, -30°C) δ 272.5 (2 x bridging C=O), 210.3 (2 x terminal CO), 171.2 (2 x ester C=O), 98.0 (2 x quaternary cyclopentadiene C), 89.7 (4 x cyclopentadiene CH), 89.4 (4 x cyclopentadiene CH), 52.5 (2 x OCH<sub>3</sub>), 32.4 (2 x alkyl CH<sub>2</sub>).

Preparation of  $[\text{Fe}(\text{C}_5\text{H}_4\text{CH}_2\text{CH}_2\text{CO}_2\text{Me})(\text{CO})_2]_2$ 

Using the above iron sandwich compound procedure,

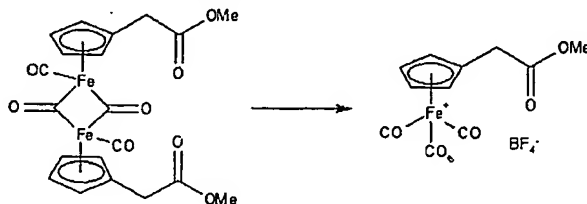
$[\text{Fe}(\text{C}_5\text{H}_4\text{CH}_2\text{CH}_2\text{CO}_2\text{Me})(\text{CO})_2]_2$  (12.75 g, 24.20 mmol, 50%) was

5 prepared as maroon-like crystals from a mixture of methyl 3-cyclopenta-1,3-dienylpropionate and methyl 3-cyclopenta-1,4-dienylpropionate (1.2:1, 14.50 g, 95.96 mmols) and diiron nonacarbonyl (34.90 g, 95.96 mmol) in degassed heptane (350 mL).

10 IR (solid)  $\nu_{\text{max}}$   $\text{cm}^{-1}$  1976 (s, terminal CO), 1937 (s, terminal CO), 1788 (s, bridging C=O), 1715 (s, ester C=O);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ , room temperature)  $\delta$  4.67 (4H, s, 4 x cyclopentadiene CH), 4.56 (4H, s, 4 x cyclopentadiene CH), 3.71 (6H, s, 2 x  $\text{OCH}_3$ ), 2.80 (4H, s, 2 x alkyl  $\text{CH}_2$ ), 2.66 (4H, s, 2 x alkyl  $\text{CH}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ,  $-30^\circ\text{C}$ )  $\delta$  4.67 (4H, s, 4 x cyclopentadiene CH), 4.57 (4H, s, 4 x cyclopentadiene CH), 3.67 (6H, s, 2 x  $\text{OCH}_3$ ), 2.76 (4H, s, 2 x alkyl  $\text{CH}_2$ ), 2.68 (4H, s, 2 x alkyl  $\text{CH}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ,  $-50^\circ\text{C}$ )  $\delta$  4.58 (8H, s, 8 x cyclopentadiene CH), 3.65 (6H, s, 2 x  $\text{OCH}_3$ ), 2.68 (8H, s, 4 x alkyl  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ , room tempearture)  $\delta$  172.7 (2 x ester C=O), 105.6 (2 x quaternary cyclopentadiene C), 88.3 (4 x cyclopentadiene CH), 87.4 (4 x cyclopentadiene CH), 51.5 (2 x  $\text{OCH}_3$ ), 34.3 (2 x alkyl  $\text{CH}_2$ ), 22.5 (2 x alkyl  $\text{CH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ ,  $-30^\circ\text{C}$ )  $\delta$  272.9 (2 x bridging C=O), 210.8 (2 x terminal CO), 173.1 (2 x ester C=O), 105.2 (2 x quaternary cyclopentadiene C), 87.9 (4 x cyclopentadiene CH), 87.0 (4 x cyclopentadiene CH), 52.1 (2 x  $\text{OCH}_3$ ), 34.3 (2 x alkyl  $\text{CH}_2$ ), 22.5 (2 x alkyl  $\text{CH}_2$ ).

## Preparation of

Tricarbonyl[methyl-2-(cyclopentadienyl)ethanoate]iron

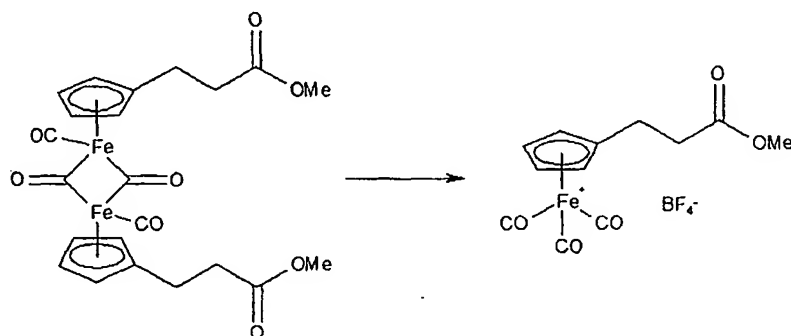
tetrafluoroborate  $[\text{Fe}(\text{C}_5\text{H}_4\text{CH}_2\text{CO}_2\text{Me})(\text{CO})_3]\text{BF}_4$  CORM-351

- 5 The following procedure was based on a modified literature method (12). Ferrocenium tetrafluoroborate (274 mg, 1.004 mmol, 2 equiv.) was added to the iron sandwich compound  $[\text{Fe}(\text{C}_5\text{H}_4\text{CH}_2\text{CO}_2\text{Me})(\text{CO})_2]_2$  (250 mg, 0.502 mmol) under nitrogen. An anhydrous mixture of degassed dichloromethane/tetrahydrofuran (33 mL; 2:1) was added and carbon monoxide was then bubbled
- 10 through the resulting reaction mixture for a period of 15 minutes. The reaction mixture was then stirred under a carbon monoxide atmosphere with bubbling of carbon monoxide through the reaction mixture after 18 and 24 hours for a period of 10
- 15 minutes. In total, the reaction mixture was stirred under a carbon monoxide atmosphere for 36 hours after which the reaction flask was flushed with nitrogen. The reaction mixture was then concentrated *in vacuo* and the resulting black solid was washed with degassed diethyl ether (5 x 20 mL),
- 20 after which the product was extracted with degassed dichloromethane (5 x 20 mL). The combined organic layers were concentrated *in vacuo* to give an orange solid which was then washed with degassed dichloromethane (20 mL). The resulting yellow solid was dissolved in acetone (20 mL), filtered and
- 25 the solvent removed *in vacuo* to give the title compound as a yellow solid (66.4 mg, 0.183 mmol, 36%).
- IR (solid)  $\nu_{\text{max}}$   $\text{cm}^{-1}$  2121 (s, terminal CO), 2065 (s, terminal CO), 1737 (s, ester CO);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ , room temperature, low concentration sample)  $\delta$  6.25 (2H, t, 2 x cyclopentadiene CH), 6.08 (2H, t, 2 x cyclopentadiene CH), 3.87 (2H, s, alkyl  $\text{CH}_2$ ), 3.77 (3H, s,  $\text{OCH}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{COCD}_3$ , room temperature, high concentration sample)  $\delta$  6.22
- 30

(2H, s, 2 x cyclopentadiene CH), 6.06 (2H, s, 2 x cyclopentadiene CH), 3.86 (2H, s, alkyl CH<sub>2</sub>), 3.77 (3H, s, OCH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>COCD<sub>3</sub>, -30°C) δ 204.7 (3 x terminal CO), 170.9 (ester C=O), 106.4 (quaternary cyclopentadiene C), 92.9 (2 x cyclopentadiene CH), 89.7 (2 x cyclopentadiene CH), 53.4 (OCH<sub>3</sub>), 32.1 (alkyl CH<sub>2</sub>).

#### Preparation of

Tricarbonyl[methyl-3-(cyclopentadienyl)propanoate]iron tetrafluoroborate [Fe(C<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me)(CO)<sub>3</sub>]BF<sub>4</sub> CORM-352



Using the ferrocenium oxidation procedure (12), [Fe(C<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me)(CO)<sub>3</sub>]BF<sub>4</sub> (95.0 mg, 0.251 mmol, 15%) was prepared as a yellow solid from iron sandwich compound [Fe(C<sub>5</sub>H<sub>4</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me)(CO)<sub>2</sub>]<sub>2</sub> (900 mg, 1.71 mmol) and ferrocenium tetrafluoroborate (933 mg, 3.42 mmol, 2 equiv.) under a carbon monoxide atmosphere for 36 hours.

IR (solid)  $\nu_{\max}$  cm<sup>-1</sup> 2059 (s, terminal CO), 2009 (s, terminal CO), 1735 (s, ester CO); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>, room temperature, low concentration sample) δ 6.15 (2H, t, 2 x cyclopentadiene CH), 6.07 (2H, t, 2 x cyclopentadiene CH), 3.67 (3H, s, OCH<sub>3</sub>), 2.94 (2H, t, alkyl CH<sub>2</sub>), 2.80 (2H, t, alkyl CH<sub>2</sub>, signal overlaps with H<sub>2</sub>O signal in CD<sub>3</sub>COCD<sub>3</sub> NMR solvent); <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>COCD<sub>3</sub>, room temperature, high concentration sample) δ 6.13 (2H, s, 2 x cyclopentadiene CH), 6.05 (2H, s, 2 x cyclopentadiene CH), 3.67 (3H, s, OCH<sub>3</sub>), 2.93 (2H, t, alkyl CH<sub>2</sub>), 2.82 (2H, t, alkyl CH<sub>2</sub>, signal overlaps with H<sub>2</sub>O signal in CD<sub>3</sub>COCD<sub>3</sub> NMR solvent); <sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>COCD<sub>3</sub>, -30°C) δ 203.7 (3 x terminal CO), 172.1 (ester C=O), 114.1 (quaternary

cyclopentadiene C), 89.4 (2 x cyclopentadiene CH), 88.8 (2 x cyclopentadiene CH), 51.4 (OCH<sub>3</sub>), 32.8 (alkyl CH<sub>2</sub>), 22.2 (alkyl CH<sub>2</sub>).

5 **Preparation of [Fe(C<sub>5</sub>H<sub>4</sub>CO<sub>2</sub>Me)(CO)<sub>3</sub>][FeCl<sub>4</sub>] CORM-357**

400 mg (0.851 mmol) of [Fe(C<sub>5</sub>H<sub>4</sub>-COOMe)(CO)<sub>2</sub>]<sub>2</sub> was dissolved in 20 ml of benzene, under argon. A solution of SO<sub>2</sub>Cl<sub>2</sub> in benzene was then added drop-wise with stirring. This resulted in the immediate formation of a yellow precipitate. The reaction was followed by IR spectroscopy, and when there was no more of the dimer starting material still present, addition was ceased. The resulting precipitate was collected on a sinter and then washed with benzene and a little cold dichloromethane (DCM). It was then recrystallised from DCM (i.e. sample dissolved in boiling DCM and then cooled to -18°C overnight). The resulting yellow crystals were isolated, washed with diethyl ether and then dried under vacuum.

101 mg (0.219 mmol) of product obtained. M<sup>r</sup> = 460.66. Yield 26%. X-ray quality crystals were obtained from a dilute solution in MeCN/diethyl ether/pentane at -18°C.

<sup>1</sup>H NMR (CD<sub>3</sub>CN): δ(ppm) v. broad due to paramagnetic counter ion

<sup>13</sup>C NMR (CD<sub>3</sub>CN): δ(ppm) 60.6 (CH<sub>3</sub>), 91.3 (ipso Cp), 97.2 (Cp), 99.8 (Cp), 161.7 (C=O), 202.7 (CO)

<sup>17</sup>O NMR (CD<sub>3</sub>CN): δ(ppm) 399.2 (CO)

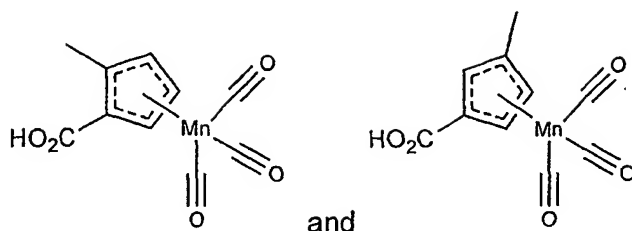
25 IR (MeCN) ν(cm<sup>-1</sup>): 2132 (s), 2089 (vs), 1745 (m)

Mass Spec (m/z): 263 (M<sup>+</sup>), 235 (M<sup>+</sup> - CO), 207 (M<sup>+</sup> - 2CO)

Elemental: Fe<sub>2</sub>C<sub>10</sub>H<sub>7</sub>O<sub>5</sub>Cl<sub>4</sub> found (calc) C: 26.14 (26.07), H: 1.62 (1.53), Cl: 30.80 (30.78)

30 **Preparation of [{MeC<sub>5</sub>H<sub>3</sub>(COOH)}Mn(CO)<sub>3</sub>] (mixture of both isomers)**

CORM-359 is a mixture of two isomers in approximately equal quantities:-



[({MeC<sub>5</sub>H<sub>3</sub>(COOH))Mn(CO)<sub>3</sub>] (mixture of both isomers)

This known compound is reported in references 19 and 20.

5 A solution of [Mn(Cp-Me)(CO)<sub>3</sub>] (1.50g, 6.88 mmol) in dry THF (15 ml) was cooled to -78°C. 1.5 eq of BuLi (6.45 ml, 10.32 mmol, 1.6M soln. in hexanes) was then added drop-wise with stirring. Stirring was continued at -78°C for 10 min, and then the reaction was allowed to warm to room temperature.

10

The solution was then poured onto a large excess of dry ice, and allowed to react until there was no solid CO<sub>2</sub> remaining. Diethyl ether was then added and the reaction poured into water. The water washing was discarded and then the organic phase extracted with three portions of 1M NaOH (aq). The combined basic aqueous extracts were then washed with two portions of diethyl ether and acidified with 10% HCl (aq). Diethyl ether was then added to dissolve the precipitated product, and the two phases separated. The organic phase was then washed with two portions of water and finally saturated brine, before being dried over MgSO<sub>4</sub>. Removal of solvent gave 512 mg (1.95 mmol) of a yellow/brown solid. Crude yield 28%.

15

A sample of this was recrystallised from hexane to give 184 mg (0.702 mmol) of a yellow solid. M<sup>r</sup> = 262.10. Recrystallised yield 10 % (although not all of sample was recrystallised).

25

<sup>1</sup>H NMR (CD<sub>2</sub>Cl<sub>2</sub>): δ(ppm) 2.05 (s, 3H Me, isomer 1, relative intensity 1.35), 2.29 (s, 3H Me, isomer 2, relative intensity 1.0), 4.79 (broad, Cp 3H), 5.38 (broad, Cp 2H), 5.49 (d J = 9.2 Hz, Cp 1H).

30

Only limited assignment possible due to broad spectrum. No differentiation possible between isomers for the Cp protons.

$^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 13.4 (Me both isomers), 80.4, 80.8 (Cp C-CO<sub>2</sub>H, 2 isomers), 81.8, 84.1, 84.7, 87.2, 87.7, 88.2 (Cp C-H, 2 isomers, 3 C per isomer) 103.5, 108.4 (Cp C-Me, 2 isomers), 171.8 (C=O broad, 2 isomers), 223.3 (CO, 2 isomers)

$^{17}\text{O}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 378.0 (CO isomer 1), 379.1 (CO isomer 2)

$^{55}\text{Mn}$  NMR ( $\text{CD}_2\text{Cl}_2$ ): Could not be obtained

IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu$ ( $\text{cm}^{-1}$ ): 2031 (s), 1948 (vs), 1727 (w), 1691 (w)

Mass Spec (m/z): 261 ( $\text{M}^-$  i.e. -  $\text{H}^+$ )

Elemental:  $\text{MnC}_{10}\text{H}_7\text{O}_5$  found (calc) C: 47.31 (45.83), H: 3.24 (2.69)

#### Preparation of $[\text{Mo}(\text{C}_5\text{H}_4\text{CO}_2\text{Me})(\text{CO})_3\text{I}]$ CORM-361

The compound  $[\text{Mo}(\text{C}_5\text{H}_4\text{CO}_2\text{Me})(\text{CO})_3\text{I}]$  was prepared using a literature method (17).

#### Preparation of $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2(\text{NO}_3)]$ CORM-380

300 mg (0.638 mmol) of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2]_2$  and 228 mg (1.34 mmol) of  $\text{AgNO}_3$  were stirred together in 15 ml of acetone at 30°C, under argon. The reaction was monitored by IR spectroscopy and after 1.5 h the reaction was shown to be complete. The solution was filtered through celite and then the solvent removed on a rotary evaporator to give a red oily residue. A silica gel column was prepared in petroleum ether (40/60). The compound was introduced as a solution in a little DCM. Elution with petroleum ether caused no band movement.

Elution with petroleum ether/diethyl ether (1:1) gave a very small amount of a yellow band. The product was eluted as a bright red band with diethyl ether. Removal of solvent on a rotary evaporator, washing with petroleum ether and drying under vacuum gave the desired solid product.

78 mg of a bright red solid was obtained (0.263 mmol).  $\text{M}^f = 297.00$ . Yield 21%. X-ray quality crystals were obtained from a diethyl ether solution at -18°C.



$^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 3.93 (s,  $\text{CH}_3$ ), 5.21 (s, Cp 2H), 5.78 (s, Cp 2H)

$^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 53.0 (Me), 82.7 (Cp), 83.9 (Cp ipso), 91.5 (Cp), 164.0 (C=O), 209.0 (CO)

5  $^{17}\text{O}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 393.7 (CO)

IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu$ ( $\text{cm}^{-1}$ ): 2076 (s), 2036 (s)

Mass Spec (m/z): No relevant peaks seen in  $\text{EI}^+$

Elemental:  $\text{FeC}_9\text{H}_7\text{NO}_7$ , found (calc) C: 35.73 (36.40), H: 2.44 (2.38), N: 4.66 (4.72)

10

**Preparation of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2\text{Br}]$  CORM-382**

400 mg (0.851 mmol) of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2]_2$  was dissolved in 20 ml of DCM, under argon. A solution of 150 mg (0.936 mmol) of  $\text{Br}_2$  in 5 ml of DCM was then added drop-wise with stirring.

15 After complete addition, stirring was continued for a further 30 min, after which time reaction was shown to be complete by IR spectroscopy.

The reaction solution was then transferred to a separating funnel and more DCM was added. It was then washed with three  
20 portions of de-oxygenated  $\text{Na}_2\text{S}_2\text{O}_3$  (aq) and once with de-oxygenated water. Then it was dried ( $\text{MgSO}_4$ ), filtered, and then the solvent removed on a rotary evaporator to give a red-brown solid. A silica gel column was prepared in petroleum ether (40/60). The product was introduced as a solution in a little  
25 DCM. The column was initially eluted with petroleum ether but this caused no movement of bands. The polarity was increased using diethyl ether, and the product was finally eluted as a dark red band with petroleum ether/diethyl ether (2:3).

Removal of solvent gave the product as a dark red solid, which  
30 was dried under vacuum.

268 mg (0.851 mmol) of product obtained.  $M^r = 314.90$ . Yield 50%. X-ray quality crystals were grown from a diethyl ether solution at  $-18^\circ\text{C}$ .

$^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 3.90 (s, Me 3H), 5.19 (s, Cp 2H), 5.70  
35 (s, Cp 2H)

$^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 52.7 (Me), 83.2 (Cp), 84.0 (Cp ipso),

90.8 (Cp), 164.3 (C=O), 210.8 (CO)

$^{17}\text{O}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 385.7 (CO)

IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu$ ( $\text{cm}^{-1}$ ): 2060 (s), 2018 (s)

Mass Spec (m/z): 314 ( $\text{M}^+$ ), 286 ( $\text{M}^+ - \text{CO}$ ), 258 ( $\text{M}^+ - 2\text{CO}$ )

5 Elemental:  $\text{FeC}_9\text{H}_7\text{O}_4\text{Br}$  found (calc) C: 34.68 (34.33), H: 2.14 (2.24), Br: 25.16 (25.37)

**Preparation of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2\text{Cl}]$  CORM-384**

500 mg (1.06 mmol) of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2]_2$  was dissolved in 14  
10 ml of dry THF, under argon. A solution of 127 mg (1.06 mmol) of  $\text{SOCl}_2$  in 5 ml dry THF was then added drop-wise with stirring. After complete addition, stirring was continued for a further 25 min. Following this, IR showed that there was still some starting material present. Hence a dilute THF  
15 solution of  $\text{SOCl}_2$  was prepared and aliquots of this were added, the reaction was stirred for 5 min, and then the IR spectrum recorded until reaction was complete. Following this, the solvent was removed on a rotary evaporator and the residue columned on silica gel. Initially prepared in petroleum ether,  
20 it was then eluted with chloroform, with the product finally being eluted as a red band with diethyl ether. Solvent was removed on a rotary evaporator and then the product recrystallised from diethyl ether/petroleum ether.  
252 mg (0.932 mmol) of a red crystalline solid was obtained.  $\text{M}^+ = 270.45$ . Yield 44%. X-ray quality crystals were grown from a more dilute diethyl ether solution, at  $-18^\circ\text{C}$ .

$^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 3.93 (s, Me 3H), 5.18 (s, Cp 2H), 5.70 (s, Cp 2H)

30  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 52.7 (Me), 83.0 (Cp), 84.5 (Cp ipso), 91.6 (Cp), 164.4 (C=O), 210.5 (CO)

$^{17}\text{O}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 386.4 (CO)

IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu$ ( $\text{cm}^{-1}$ ): 2064 (s), 2022 (s)

Mass Spec (m/z): 270 ( $\text{M}^+$ ), 242 ( $\text{M}^+ - \text{CO}$ ), 214 ( $\text{M}^+ - 2\text{CO}$ )

35 Elemental:  $\text{FeC}_9\text{H}_7\text{O}_4\text{Cl}$  found (calc) C: 39.77 (39.97), H: 2.34 (2.61), Cl: 12.94 (13.11)

**Preparation of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2\text{I}]$  CORM-391**

- 800 mg (1.70 mmol) of  $[\text{Fe}(\text{C}_5\text{H}_4\text{-CO}_2\text{Me})(\text{CO})_2]_2$  was dissolved in 40 ml of DCM, under argon. A solution of 497 mg (1.96 mmol) of  $\text{I}_2$  in 20 ml of DCM was then added drop-wise with stirring. After  
5 complete addition, stirring was continued for a further 3 h, after which time reaction was shown to be complete by IR spectroscopy. The reaction solution was then transferred to a separating funnel and more DCM was added. It was then washed with three portions of de-oxygenated  $\text{Na}_2\text{S}_2\text{O}_3$  (aq) and once with  
10 de-oxygenated water. It was then dried ( $\text{MgSO}_4$ ), filtered, and then the solvent removed on a rotary evaporator to give a black solid. This was dried under vacuum.  
1.03 g of product obtained.  $M^r = 361.90$ . Yield 84%. X-ray quality crystals were obtained from a diethyl ether solution  
15 at  $-18^\circ\text{C}$ .  
 $^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 3.90 (s, Me 3H), 5.13 (s, Cp 2H), 5.72 (s, Cp 2H)  
 $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 52.6 (Me), 83.7 (Cp), 89.9 (Cp), 164.2 (C=O), 212.0 (CO)  
20  $^{17}\text{O}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$ (ppm) 384.9 (CO)  
IR ( $\text{CH}_2\text{Cl}_2$ )  $\nu(\text{cm}^{-1})$ : 2050 (s), 2010 (s)  
Mass Spec (m/z): 362 ( $M^+$ ), 334 ( $M^+ - \text{CO}$ ), 306 ( $M^+ - 2\text{CO}$ )  
Elemental:  $\text{FeC}_9\text{H}_7\text{O}_4\text{I}$  found (calc) C: 29.86 (29.87), H: 1.71 (1.95), I: 35.06 (35.07)  
25 This compound is reported in Reference 18.

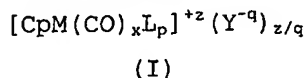
## References:

1. Piantadosi CA. Toxicity of carbon monoxide: hemoglobins vs. histotoxic mechanisms. In: Carbon monoxide. (Edited by Penney DG). 1996; Chapter 8.
- 5 2. Sjostrand T. Endogenous formation of carbon monoxide in man under normal and pathological conditions. Scan J Clin Lab Invest 1949 ; 1 : 201-14.
- 10 3. Coburn RF, Blakemore WS, Forster RE. Endogenous carbon monoxide production in man. J Clin Invest 1963 ; 42 : 1172-8.
- 15 4. Coburn RF, Williams WJ, Forster RE. Effect of erythrocyte destruction on carbon monoxide production in man. J Clin Invest 1964; 43: 1098-103.
- 20 5. Coburn RF, Williams WJ, Kahn SB. Endogenous carbon monoxide production in patients with hemolytic anemia. J Clin Invest 1966 ; 45: 460-8.
6. Sjostrand T. The formation of carbon monoxide by in vitro decomposition of haemoglobin in bile pigments. Acta Physiol Scand 1952 ; 26: 328-33.
- 25 7. Coburn RF, Williams WJ, White P, Kahn SB. The production of carbon monoxide from hemoglobin in vivo. J Clin Invest 1967 ; 46: 346-56.
- 30 8. Tenhunen R, Marver HS, Schmid R. Microsomal heme oxygenase. Characterization of the enzyme. J Biol. Chem. 1969 ; 244: 6388-94.
- 35 9. Scharf SM, Permutt S, Bromberger-Barnea B. Effects of hypoxic and CO hypoxia on isolated hearts. J Appl Physiol 1975 ; 39: 752-8.

10. G. L. Grunewald and D. P. Davis. *J. Org. Chem.*, 1978, 43, 3074.
11. N. J. Coville, M. S. Loonat, D. White and L. Carlton,  
5 *Organometallics*, 1992, 11, 1082.
12. D. Catheline and D. Astruc, *Organometallics*, 1984, 3, 1094-1100.
- 10 13. H. H. Hammud and G. M. Moran, *J. Organomet. Chem.*, 1986, 307, 255.
14. E.S. Hand, S.C. Johnson and D.C. Baker, *J. Org. Chem.*, 1997, 62, 1348-1355.
- 15 15. P.-H. Yeh, Z. Pang and R.F. Johnston, *J. Organomet. Chem.*, 1996, 509, 123-129.
16. R.A.L. Gendron, D.J. Berg and T. Barclay, *Can. J. Chem.*,  
20 2002, 80, 1285-1292.
17. A. Chaloyard, N. el Murr, *Inorg. Chem.*, 1980, 18, 3217.
18. N. J. Coville, M. S. Loonat, D. White and L. Carlton,  
25 *Organometallics*, 1992, 11, 1082.
19. P. Hublau, C. Sergheraert, L. Ballester and M. Dautrevaux, *Eur. J. Med. Chem.*, 1983, 18, 131.
- 30 20. M. Le Plouzennec, F. Le Moigne and R. Dabard, *J. Organomet. Chem.*, 1977, 132, 409.

Claims

1. A pharmaceutical composition for delivery of CO,  
comprising as an active ingredient a compound represented by  
5 formula (I) or formula (II) below:



wherein:-

- M is a transition metal selected from group 6, 7, 8 or 9 of  
10 the periodic table;

Y is a counteranion;

q is the charge of Y and is selected from 1, 2 or 3;

x is 2, 3 or 4;

- z is 0 or 1, and x, z and p satisfy the equation  
15  $13 - g = 2x - z + p$

where g is the group number of M in the periodic table, and  
where

p is 0 or 1 when g is 6; or

p is 0 when g is 7, 8 or 9;

- 20 L is a ligand selected from H, halide, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl,  
C<sub>1-7</sub> alkoxy, C<sub>6-14</sub> aryloxy, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, acyloxy  
(-OC(=O)R<sup>5</sup>), amido (-C(=O)NR<sup>5</sup>R<sup>6</sup>), acylamido (-NR<sup>5</sup>C(=O)R<sup>6</sup>),  
aminocarbonyloxy (-OC(=O)NR<sup>5</sup>R<sup>6</sup>) and aminothiocabonylthiol  
(-SC(=S)NR<sup>5</sup>R<sup>6</sup>);

- 25  $[\text{CpM}'(\text{CO})_2\text{L}']^{+z}(\text{Y}^{-q})_{z/q}$   
(II)

wherein

M' is Fe or Ru;

Y is a counteranion;

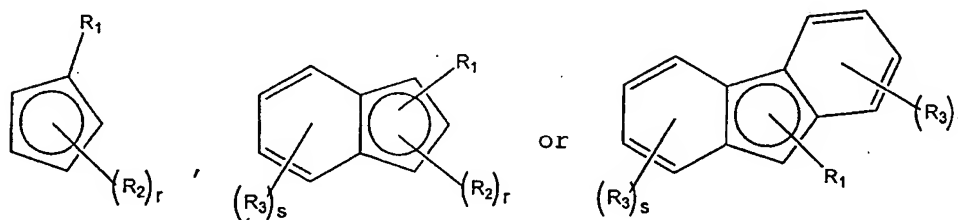
- 30 q is the charge of Y and is selected from 1, 2 or 3;

L' is a ligand selected from either

- a first group consisting of H, halide, -NO<sub>2</sub>, -ONO, -ONO<sub>2</sub>,  
-OH, -SCN, -NCS, -OCN, -NCO, C<sub>1-7</sub> alkyl, C<sub>6-14</sub> aryl, C<sub>1-7</sub> alkoxy,  
C<sub>6-14</sub> aryloxy, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, acyloxy (-OC(=O)R<sup>7</sup>),  
35 amido (-C(=O)NR<sup>7</sup>R<sup>8</sup>), acylamido (-NR<sup>7</sup>C(=O)R<sup>8</sup>), aminocarbonyloxy  
(-OC(=O)NR<sup>7</sup>R<sup>8</sup>), (SC(=O)R<sup>7</sup>), -SC(S)R<sup>7</sup>, -SC(S)OR<sup>7</sup>, -SC(O)NR<sup>7</sup>R<sup>8</sup>,

-SC(O)OR<sup>7</sup>; aminothiocarbonylthiol (-SC(=S)NR<sup>7</sup>R<sup>8</sup>), -OC(=S)R<sup>7</sup>,  
 -N(C(=O)R<sup>7</sup>)<sub>2</sub>, and -C(O)(OR<sup>7</sup>); -O-PR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>, -O-PR<sup>7</sup><sub>(3-n)</sub>(OR<sup>8</sup>)<sub>n</sub> where  
 n=1, 2 or 3, -O-PR<sup>7</sup><sub>(3-n)</sub>(NR<sup>8</sup>R<sup>9</sup>)<sub>n</sub> where n=1, 2 or 3; or

- a second group consisting of OR<sup>7</sup>R<sup>8</sup>, O=CR<sup>7</sup>R<sup>8</sup>, O=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>,  
 5 O=C(OR<sup>7</sup>)R<sup>8</sup>, O=SR<sup>7</sup>R<sup>8</sup>, O=S(O)R<sup>7</sup>R<sup>8</sup>, SR<sup>7</sup>R<sup>8</sup>, S(O)R<sup>7</sup>R<sup>8</sup>, S=CR<sup>7</sup>R<sup>8</sup>,  
 S=C(NR<sup>7</sup>R<sup>8</sup>)R<sup>9</sup>, S=C(OR<sup>7</sup>)R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>, NCR<sup>7</sup>, N\* where N is an aromatic  
 nitrogen atom in an aromatic ring represented by N\*, PR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>,  
 PR<sup>7</sup><sub>(3-n)</sub>(OR<sup>8</sup>)<sub>n</sub> where n=1, 2 or 3,  
 PR<sup>7</sup><sub>(3-n)</sub>(NR<sup>8</sup>R<sup>9</sup>)<sub>n</sub> where n=1, 2 or 3, O=PR<sup>7</sup>R<sup>8</sup>R<sup>9</sup>, O=PR<sup>7</sup><sub>(3-n)</sub>(OR<sup>8</sup>)<sub>n</sub> where  
 10 n=1, 2 or 3, O=PR<sup>7</sup><sub>(3-n)</sub>(NR<sup>8</sup>R<sup>9</sup>)<sub>n</sub> where n=1, 2 or 3;  
 R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are independently selected from H, optionally  
 substituted C<sub>1-7</sub> alkyl and optionally substituted C<sub>6-20</sub> aryl,  
 with the proviso that any two of R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> which are both  
 attached to the same O, N or S atom may, taken together with  
 15 that atom, form an optionally substituted heterocyclic ring  
 having 5, 6 or 7 ring atoms;  
 z=0 when L' is from said first group and z=1 when L' is from  
 said second group;  
 and wherein in formula (I) and formula (II):-  
 20 Cp is selected from:



where r, s and t are each independently selected from 1, 2, 3  
 or 4; and

R<sub>1</sub> is either:

- [Alk]<sub>n</sub>-O-C(O)-Q<sub>1</sub>, -[Alk]<sub>n</sub>-C(O)-O-Q<sub>1</sub>, -[Alk]<sub>n</sub>-NR<sub>4</sub>-C(O)-Q<sub>1</sub> or  
 25 -[Alk]<sub>n</sub>-C(O)-NQ<sub>1</sub>Q<sub>2</sub>,

n is 0 or 1;

Alk is a C<sub>1-28</sub> alkylene group;

- Q<sub>1</sub> and Q<sub>2</sub> are each independently selected from H, optionally  
 substituted C<sub>1-22</sub> alkyl and an optionally substituted C<sub>6-25</sub> aryl  
 30 group;

each  $R_2$  is independently selected from  $R_1$ , H,  $C_{1-22}$  alkyl,  $C_{6-25}$  aryl,  $C_{1-7}$  alkoxy,  $C_{5-10}$  aryloxy, halide, formyl,  $C_{1-7}$  alkylacyl and  $C_{6-20}$  arylacyl;

$R_4$  is selected from H,  $C_{1-22}$  alkyl and  $C_{6-25}$  aryl;

- 5 each  $R_3$  is independently selected from H, hydroxy, nitro, cyano, halide, sulfhydryl,  $C_{1-22}$  alkyl,  $C_{6-25}$  aryl,  $C_{1-7}$  alkoxy,  $C_{5-10}$  aryloxy, formyl,  $C_{1-7}$  alkylacyl,  $C_{6-20}$  arylacyl,  $C_{1-7}$  alkylthio,  $C_{5-10}$  arylthio, carboxylic acid ( $-C(=O)OH$ ), ester ( $-C(=O)OR^5$ ), acyloxy ( $-OC(=O)R^5$ ), amido ( $-C(=O)NR^5R^6$ ), acylamido ( $-NR^5C(=O)R^6$ ) and amino ( $-NR^5R^6$ ); and
- 10  $R^5$  and  $R^6$  are independently selected from H,  $C_{1-7}$  alkyl and  $C_{6-20}$  aryl.

2. A pharmaceutical composition according to claim 1,  
15 wherein M or M' is Fe.

3. A pharmaceutical composition according to claim 1,  
wherein said compound is represented by formula (I) and z is  
1.

- 20 4. A pharmaceutical composition according to claim 1, 2 or 3, wherein Y is selected from halide, sulphonate, borate, hexafluorophosphate, perhalate, sulphate, phosphate, a carboxylate anion of an organic acid or of an amino acid.

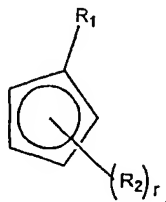
- 25 5. A pharmaceutical composition according to claim 1 or claim 2, wherein said compound is represented by formula (I) and g is 6 and p is 1.

- 30 6. A pharmaceutical composition according to claim 5, wherein L is selected from H, halide,  $C_{1-7}$  alkyl,  $C_{6-14}$  aryl,  $C_{1-7}$  alkoxy and  $C_{6-14}$  aryloxy.

7. A pharmaceutical composition according to claim 1,  
35 wherein said compound is represented by formula (II) and L' is selected from halide and  $-ONO_2$ .



8. A pharmaceutical composition according to any one of claims 1 to 7, wherein Cp is

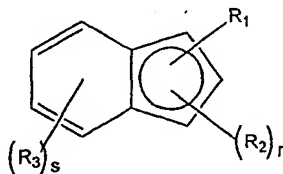


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9. A pharmaceutical composition according to claim 8, wherein r is 1 or 4.

10. A pharmaceutical composition according to any one of claims 1 to 7, wherein Cp is

10



11. A pharmaceutical composition according to claim 10, wherein r is 1.

15

12. A pharmaceutical composition according to claim 10 or claim 11, wherein s is 1, 2 or 3.

13. A pharmaceutical composition according to any one of claims 1, 10, 11 or 12, wherein R<sub>3</sub> is selected from H, hydroxy, nitro, cyano, halide, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy and amino (-NR<sup>5</sup>R<sup>6</sup>).

20

14. A pharmaceutical composition according to any one of the preceding claims, wherein R<sub>2</sub> is identical to R<sub>1</sub>.

25

15. A pharmaceutical composition according to any one of claims 1 to 13, wherein R<sub>2</sub> is selected from H, C<sub>1-22</sub> alkyl and C<sub>9-25</sub> aryl.

30

16. A pharmaceutical composition according to any one of claims 1 to 15, wherein  $R_1$  is  $-[Alk]_n-O-C(O)-Q_1$  unit and  $n$  is 1.

17. A pharmaceutical composition according to claim 16, wherein  $Q_1$  is selected from H, substituted  $C_{1-22}$  alkyl and optionally substituted  $C_{6-25}$  aryl group.

18. A pharmaceutical composition according to claim 17, wherein the substituent in said substituted  $C_{1-22}$  alkyl and said optionally substituted  $C_{6-25}$  aryl group is selected from  $\alpha$ -amino acid, hydroxy, ether, ester, oxo, acyloxy, amino, amido and acylamido.

19. A pharmaceutical composition according to any one of claims 1 to 15, wherein  $R_1$  is  $-[Alk]_n-C(O)-O-Q_1$  and  $n$  is 1.

20. A pharmaceutical composition according to claim 19, wherein  $Q_1$  is selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl.

21. A pharmaceutical composition according to any one of claims 1 to 15, wherein  $-[Alk]_n-C(O)-O-Q_1$  and  $n$  is 0.

22. A pharmaceutical composition according to claim 21, wherein  $Q_1$  is selected from H, optionally substituted  $C_{1-22}$  alkyl and an optionally substituted  $C_{6-25}$  aryl group.

23. A pharmaceutical composition according to any one of claims 1 to 22 adapted for delivery by an oral, intravenous, transdermal, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal or suppository route.

24. A compound according to formula (III)

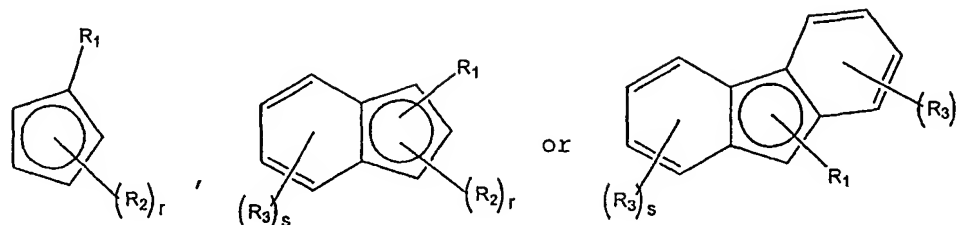


wherein

Y is a counteranion;

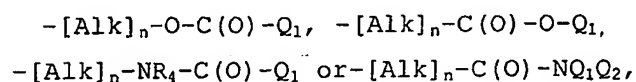
q is the charge of Y and is selected from 1, 2 or 3; and

Cp is selected from:



5 where r, s and t are each independently selected from 1, 2, 3 or 4; and

R<sub>1</sub> is either:



10 n is 0 or 1;

Alk is a C<sub>1-28</sub> alkylene group;

Q<sub>1</sub> and Q<sub>2</sub> are each independently selected from H, optionally substituted C<sub>1-22</sub> alkyl and an optionally substituted C<sub>6-25</sub> aryl group;

15 each R<sub>2</sub> is independently selected from R<sub>1</sub>, H, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy, halide, formyl, C<sub>1-7</sub> alkylacyl and C<sub>6-20</sub> arylacyl;

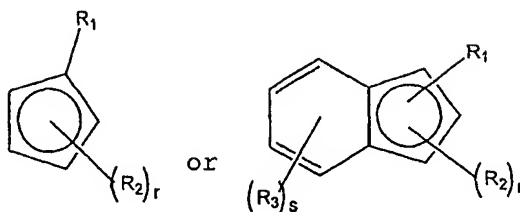
R<sub>4</sub> is selected from H, C<sub>1-22</sub> alkyl and C<sub>6-25</sub> aryl;

20 each R<sub>3</sub> is independently selected from H, hydroxy, nitro, cyano, halide, sulfhydryl, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy, formyl, C<sub>1-7</sub> alkylacyl, C<sub>6-20</sub> arylacyl, C<sub>1-7</sub> alkylthio, C<sub>5-10</sub> arylthio, carboxylic acid (-C(=O)OH), ester (-C(=O)OR<sup>5</sup>), acyloxy (-OC(=O)R<sup>5</sup>), amido (-C(=O)NR<sup>5</sup>R<sup>6</sup>), acylamido (-NR<sup>5</sup>C(=O)R<sup>6</sup>) and amino (-NR<sup>5</sup>R<sup>6</sup>); and

25 R<sup>5</sup> and R<sup>6</sup> are independently selected from H, C<sub>1-7</sub> alkyl and C<sub>6-20</sub> aryl.

25. A compound according to claim 24, wherein R<sub>3</sub> is selected from H, hydroxy, nitro, cyano, halide, C<sub>1-22</sub> alkyl, C<sub>6-25</sub> aryl, C<sub>1-7</sub> alkoxy, C<sub>5-10</sub> aryloxy and amino (-NR<sup>5</sup>R<sup>6</sup>).

26. A compound according to claim 24 or claim 25, wherein Cp is



27. A compound according to any one of claims 24 to 26, wherein  $R_1$  is  $-[Alk]_n-O-C(O)-Q_1$  or  $-[Alk]_n-C(O)-O-Q_1$  and where  $n$  is 0.
28. A compound according to claim 27, wherein  $Q_1$  is selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl.
29. A compound according to claim 28, wherein the optional substituent in said optionally substituted  $C_{1-10}$  alkyl and said optionally substituted  $C_{6-14}$  aryl group is selected from  $C_{1-10}$  alkyl,  $C_{6-14}$  aryl,  $\alpha$ -amino acid group, hydroxy, ether, ester, oxo, acyloxy, amino, amido and acylamido.
30. A compound according to any one of claims 24 to 26, wherein  $R_1$  is  $-[Alk]_n-O-C(O)-Q_1$  or  $-[Alk]_n-C(O)-O-Q_1$  and  $n$  is 1.
31. A compound according to claim 30, wherein Alk is a linear or branched saturated  $C_{1-10}$  alkylene group.
32. A compound according to claim 30 or 31, wherein  $Q_1$  is selected from H, optionally substituted  $C_{1-10}$  alkyl and optionally substituted  $C_{6-14}$  aryl.
33. A compound according to any one of claims 24 to 32, wherein Y is selected from halide, sulphonate, borate,

hexafluorophosphate, perhalate, sulphate, phosphate, a carboxylate anion of an organic acid or of an amino acid.

34. A method of introducing CO to a mammal as a  
5 physiologically effective agent comprising the step of administering a pharmaceutical composition according to any one of claims 1 to 23, said compound requested by formula (I) or formula (II) being capable of releasing CO when administered.
- 10 35. A method according to claim 34, for stimulating neurotransmission or vasodilation, or for the treatment of any hypertension, radiation damage, endotoxic shock, inflammation, an inflammatory-related disease, hyperoxia-induced injury,  
15 apoptosis, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction and adult respiratory distress syndrome.
- 20 36. A method of treatment of an extracorporeal or isolated organ, comprising contacting the organ with a pharmaceutical composition according to any one of claims 1 to 23.
- 25 37. A method according to claim 36, wherein the metal carbonyl makes available carbon monoxide (CO) to limit post-ischemic damage.
- 30 38. A method according to claim 37, wherein said organ is extracorporeal.
39. A method according to claim 37, wherein said organ is inside or attached to the body but isolated from the blood supply.
- 35 40. A method according to any one of claims 36 to 39, wherein the contacting step includes perfusing said organ with said

composition.

41. Use of a compound according to any one of claims 24 to 33 for stimulating neurotransmission or vasodilation, or for the treatment of any hypertension, radiation damage, endotoxic shock, inflammation, an inflammatory-related disease, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction and adult respiratory distress syndrome.

42. Use of a compound according to claim 41 for treatment of an isolated organ to limit post-ischemic damage in an isolated organ which is inside or attached to the body but isolated from the blood supply.

43. Use of a compound according to any one of claims 24 to 33, in the manufacture of a medicament for administration by an oral, intravenous, subcutaneous, nasal, inhalatory, intramuscular, intraperitoneal or suppository route, for the stimulation of neurotransmission or vasodilation by CO as a physiologically effective agent, or for the treatment of any hypertension, radiation damage, endotoxic shock, inflammation, an inflammatory-related disease, hyperoxia-induced injury, apoptosis, cancer, transplant rejection, arteriosclerosis, post-ischemic organ damage, myocardial infarction, angina, haemorrhagic shock, sepsis, penile erectile dysfunction and adult respiratory distress syndrome.

44. A kit for producing a pharmaceutical solution, comprising a compound according to any one of claims 24 to 33 in solid form and a pharmaceutically acceptable solvent.

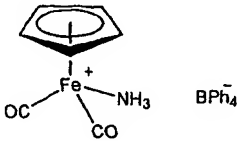
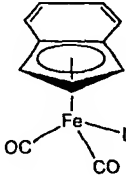
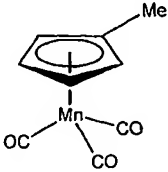
Compound	Structure	MW	Kinetics of CO Release (min)	Notes
CORM-303		513	> 3000	Soluble in EtOH
CORM-343		440.73	>3000	-
CORM-360		218.09	>3000	Soluble in EtOH

Figure 1

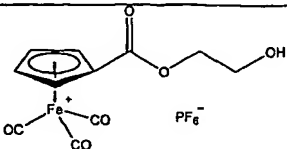
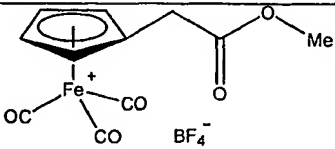
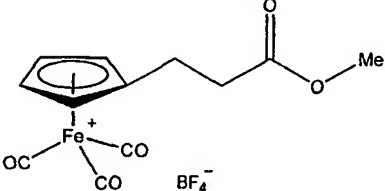
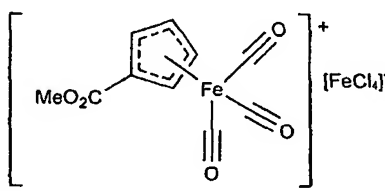
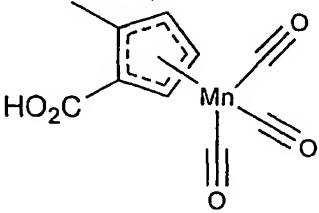
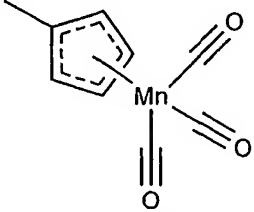
Compound	Chemical Structure	Molecular Weight	Kinetics of CO Release (min)	Cytotoxicity	Anti-inflammatory action	Solubility
CORM-337		438	62 ± 6	V	*	H <sub>2</sub> O
CORM-351		363.8	225 ± 20	V	***	H <sub>2</sub> O
CORM-352		377.8	285 ± 30	V	***	H <sub>2</sub> O
CORM-357		461	42 ± 5 min	V	**	H <sub>2</sub> O
CORM-359		262.1	3000±300 min	N.D.	N.D.	Ethanol Slight water solubility at pH 7.4
CORM-360		218.09	>3000 min	N.D.	N.D.	Ethanol

Figure 2 (continued on next sheet)



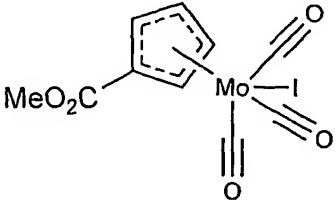
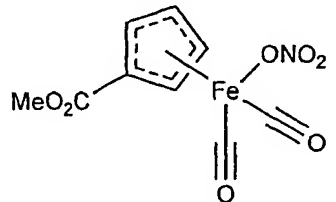
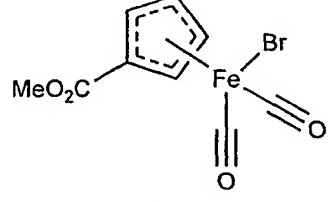
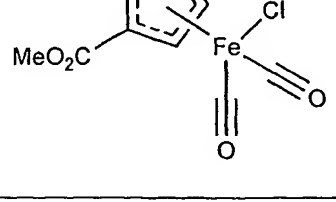
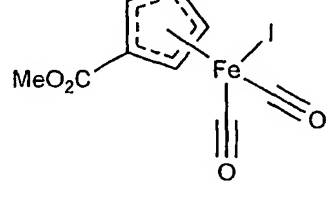
Compound	Chemical Structure	Molecular Weight	Kinetics of CO Release (min)	Cytotoxicity	Anti-inflammatory action	Solubility
CORM-361		430	58±6 min	V	***	Ethanol
CORM-380		297	170	V	**	H <sub>2</sub> O
CORM-382		314.9	38	V	**	H <sub>2</sub> O
CORM-384		270.45	63	V	**	Ethanol Slight water solubility at pH 7.4
CORM-391		361	48	V	***	Ethanol

Figure 2 (continued)